SHOCK

Its Dynamics, Occurrence and Management

By VIRGIL H MOON, A B , M Sc , M D
Professor of Pathology Jefferson Medical College Philadelphia

ILLUSTRATED WITH 36 ENGRAVINGS



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To My Friend

WALTER BRADFORD CANNON

Whose early interpretations I have been gratified to corroborate and to extend

PREFACE

THE phenomena of shock have both fascinated and baffled the medical profession for more than a century. The interest in it is increased manifold during times of war but even in civil life the occurrence of traumatic injuries from industrial and other accidents makes the recognition and management of shock a problem. The interest of surgeons will continue so long as man is subject to physical injuries and so long as operative surgery is practiced.

It is now recognized that this type of circulatory failure occurs in a wide variety of conditions other than physical trauma. This fact makes it imperative that internists and men in other fields of medicine have both a theoretic and a practical knowledge of this phenomenon. Failure to understand its mechanism, its conditions of occurrence, its early recognition, its prevention and treatment inevitably will result in failure to cope with it.

The past decade has been unusually fruitful, both in precise information concerning the mechanism of shock and its early recognition, and in the development of more effective means for combating it. The need for a condensed practical treatise embodying all these features requires no further emphasis. These chapters are offered in an attempt to meet that need.

Many busy physicians lack time for extensive reading. For the convenience of such, most of the chapters close with a short summary indicating the significance of the subject matter presented and the author's interpretation of it.

We shall not review in detail the numerous attempts to explain the phenomena of shock and we shall summarize only briefly the resulting contributions of factual evidence. But we shall inquire why diligent and conscientious efforts have led to divergent interpretations. An analysis of the causes for disagreement may be more illuminating than a reëxamination of the existing data.

The vascular reactions which underlie the phenomena of shock were discussed in a former treatise, *Shock and Related Capillary Phenomena* (Oxford University Press, New York, 1938). Readers interested in the mechanism of inflammation, edema and the localization of infections will find discussions and references there which

are not cited here It is gratifying to note that subsequent developments have not modified but have corroborated the interpretations set forth there These chapters present a continuation from where that treatise left off, but since this work must portray the *entire* picture, it is necessary to chart ground previously surveyed The relationships depicted there integrate smoothly with recent acquisitions of knowledge These include Disturbances of fluid balance physiologically related to shock, the origin and significance of the associated blood chemical changes, similarities and distinctions between shock and the effects of hemorrhage, the effects of radiant energy, disturbances of renal function, and others

The physiologic and pathologic features of shock, its dynamics, its conditions of occurrence, blood chemical changes, similarities and distinctions between shock and the effects of hemorrhage, disturbances of renal function, and others, are given detailed consideration in Part I Part II deals exclusively with practical matters including prevention, early recognition, diagnosis and management One chapter sets forth the most recent developments in the use of transfusions, plasma, serum and blood substitutes in the treatment of hemorrhage and of shock

I gratefully acknowledge indebtedness to my associates for their steadfast cooperation both in developing and in recording the material presented here—to Drs David R Morgan, Marshall M Lieber and Donald McGrew for efficient collaboration in pathologic and experimental studies, and to Miss Mary T Kelly for patient and tireless clerical assistance

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SHOCK

Its Dynamics, Occurrence and Management

PART I

The Vascular Dynamics of Shock

FOREWORD

Few conditions of disease have been subjected to more diversified or penetrating investigation than has shock, yet final agreement concerning its nature and mechanism has been delayed. For more than a decade, my associates and I have retraced the trails left by others in this field and have made a few excursions into regions not hitherto explored. From these experiences the conviction has emerged that four major causes are responsible for the confused interpretations of shock

1. *Deficiency of knowledge concerning capillary reactions and functions*
2. *A belief in the identity of shock with the effects of hemorrhage*
3. *Unrecognized sources of error in experimental technique*
4. *Failure to investigate the problem by the methods which pathologists use*

An analysis of these causes for disagreement, and of evidence resulting from the efforts of other workers, may clarify some of the uncertainties which have surrounded this subject. It is the author's belief that such an analysis may dispel much of the confusion and may contribute to a clearer understanding of the mechanism of shock and of its associated phenomena.

CHAPTER I

THE CAPILLARIES[1]

THE enormously important functions of the capillaries in the economic order of the body have not been understood until recently Likewise pathologic processes originating in the capillaries have not been recognized hitherto These two phases are combined inseparably in several disorders of the circulation A brief summary of endothelial functions and of capillary reactions is essential to a comprehension of the pathologic physiology of shock Moot questions and minutiæ will be omitted and only those interpretations will be set forth concerning which there is agreement among students of capillary physiology

CAPILLARY PHYSIOLOGY

Tissues during functional activity require 20 to 40 times as much blood as the same tissues at rest Each tissue and organ has a capillary supply adequate to its maximum need which is far in excess of its requirement when at rest If the entire capillary stream bed of the skeletal muscles were open to a normal diameter simultaneously, approximately the entire blood volume of the body would be required to fill it Other areas, as the gastrointestinal tract, the respiratory tract or the parenchymatous organs, have a total capillary supply perhaps of equal magnitude to that of the muscles From these considerations it becomes apparent what a serious circulatory disturbance might result if the capillary bed of a large visceral area should become relaxed and open to circulation simultaneously

The chief functions of the blood—supplying oxygen and other substances to the tissue cells and the elimination of waste products —are accomplished by diffusion through the capillary endothelium *A mere increase in the arterial blood flow to an organ does not fill* its circulatory requirements The metabolic needs of the cells are served only when the blood is spread upon the surface of the capillary endothelium The area of this diffusion membrane

[1] AUTHOR'S NOTE —Part of the subject matter in this chapter is condensed from several chapters of *Shock and Related Capillary Phenomena*, New York, Oxford Press, 1938 Readers desiring a more detailed analysis of capillary reactions will find references there which are not cited here

must be increased in a degree proportionate to the increased metabolic activity Krogh showed that the capillary tubes are so finely drawn that within them 1 cc of blood is in contact with from 5000 to 7000 sq cm of endothelial surface If one can imagine 16 drops of fluid evenly spread upon 4 or 5 square feet of surface, he may sense the physiologic efficiency with which a minimum volume of blood is spread upon a maximum area of the diffusion membrane

The mechanism by which both the distribution of blood and the area of diffusion surface are adjusted to the needs of the cells is marvelous in its delicacy and adaptability Nerve control is a minor factor in this mechanism, the major factor is the direct reaction of the capillaries to minute alteration in biochemical

NORMAL CAPILLARY REACTION

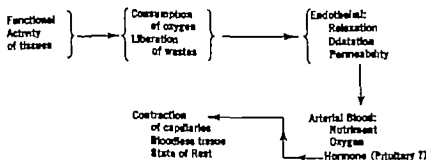


FIG. 1 —This diagram illustrates the sequence of physiologic reactions by which the local capillary circulation is adapted to the needs of the cells.

concentrations. The capillaries are not simple collapsible tubes, for their walls have tonus and contractility independent of the adjacent arteries and veins and in resting tissues, most of the capillaries are contracted and bloodless Functioning cells consume oxygen and liberate products of metabolism to which the capillary endothelium is delicately susceptible The walls relax and the endothelium becomes more permeable whenever moderate anoxia develops. This relaxation both increases the area of endothelial surface and allows an increased flow of arterial blood, supplying oxygen and other nutrients Fresh arterial blood contains a hormonal substance perhaps of pituitary origin, which causes the capillaries again to contract This limits the flow of blood until lack of oxygen and the accumulation of metabolites again cause relaxation Thus the circulatory cycle in the indi-

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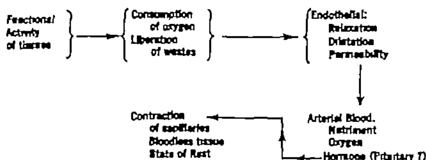


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vidual capillaries is repeated at a rate directly commensurate with the functional activity of the cells (see Fig 1) This constitutes a self-regulating mechanism which serves a double purpose it distributes blood locally in proportion to the needs of cells, at the same time it adjusts the area of diffusion surface—the endothelial wall—through which the needed substances may reach the cells In the highly efficient economy of normal circulation, no excess supply and no unfilled demand exist The supply is adjusted to the demand with delicate accuracy

The response of endothelium to cytoplasmic substance and to metabolic products is like that resulting from lack of oxygen Ebbecke showed that cytoplasmic substance, released from cells either as a result of functional activity or of any kind of irritation to the cells, causes dilatation of the adjacent capillaries This reaction followed mild injury to cells by mechanical, thermal, chemical, electrical and toxic agents The subsequent investigations of Lewis confirmed those of Ebbecke The cytoplasmic substance, given off as described, caused dilatation and engorgement of capillaries and increased the permeability of the endothelium This allowed plasma to transude into the tissue spaces, resulting in local edema He called this the "*triple response*" and stated that, whenever and however it occurred, it resulted from the action of "H-substance" derived from the cytoplasm of cells These investigations furnish an acceptable explanation for the hyperemia and edema which follow injury to tissues and which precede the development of inflammation

Ebbecke showed also that cells give off minute amounts of cytoplasmic substance during, and as a result of, functional activity. Other physiologists have stated that functional activity increases the permeability of the cell wall or surface, this would allow the escape of cytoplasmic fluid as stated by Ebbecke This fluid substance effects the adjacent capillary walls as described above and is believed to cause functional hyperemia It appears that lack of oxygen and products of the physiologic activity of cells are the agents responsible for the normal dilatation of capillaries present in *functional hyperemia* Inflammatory hyperemia is a similar response of the endothelium to substances given off when cells are injured

The Formation and Flow of Lymph.—Fluids derived from the plasma of the blood and from the metabolic activity of cells, constitute the tissue fluid The watery portion of this, and its content of crystalloids and diffusible substances, may be reab-

sorbed into the blood through the diffusion membrane—the capillary walls. The remainder, including colloids and other non-diffusible substances, finds its way into the lymphatic capillaries and constitutes the lymph. The volume of lymph flowing from an area of tissue is increased by conditions which increase the formation of tissue fluid. These include physiologic activity of the tissue, an increase in venous or capillary blood pressure, a decrease in plasma protein,[1] and *increased permeability of the capillary endothelium*.

Heidenhain (1891) noted that commercial peptone would produce a decline in blood pressure accompanied by an increased flow of lymph when given intravenously to dogs. He found that extracts of various marine animals and of normal tissues, as liver, pancreas, mucosa, muscle and others produced the same effects. He noted in such experiments that both the volume and the protein content of the lymph were increased and that the plasma volume of the blood was decreased while its total solids were increased—a change now designated by the term *hemoconcentration* (see Part II, Chapter XX). He stated that concentration of the blood was characteristic of the effects of these "lymphagogues of the 1st class" and attributed those effects to increased secretory activity of the endothelium.

Investigating the phenomena described by Heidenhain, Starling showed that these "lymphagogues" in each case were general poisons which affected especially the capillary walls and altered their semipermeable quality, resulting in the leakage of fluid from the blood into the tissue spaces. This explanation was confirmed by subsequent studies on endothelial function and reactions (Krogh, Ebbecke, Lewis, Landis, Drinker). The increased flow of lymph, its high protein content, the declining blood pressure, the decreased plasma volume and the hemoconcentration result from the leakage of plasma through endothelium rendered abnormally permeable by the effects of the agents used. Many other substances have since been shown to produce the effects described. These include certain alkaloids, diphtheria toxin, tuberculin and other bacterial products, foreign proteins and products of protein cleavage, histamine, bile and cholic salts, venoms, and many drugs, chemicals and poisons. The agents mentioned, and many others not listed, have one property in common—that of producing relaxation and increased permeability of capillary endothelium. Numerous instances of these effects are cited in Chapters VII, XII and XIII.

certain ions, as Na, K chlorides and other constituents Both barriers *between the compartments are freely permeable to water* their impermeability to other substances is not absolute but fluctuates physiologically within limits For example capillary endothelium allows the passage of small amounts of plasma protein (Drinker), varying amounts of which may be found in the tissue fluid and lymph This permeability increases during functional activity of the tissue cells and diminishes during rest But the quality of semipermeability, manifested both by the endothelial membrane and by the outer cytoplasmic surface of cells, is *absolutely essential* to the operation of the force known as *osmotic pressure* Hence variations in permeability beyond physiologic limits will render ineffective the mechanism of fluid balance

The physiologic control of the quality of permeability both vascular and cellular, appears to be a function of the adrenal cortical hormone Lack of this hormone results in increased permeability both of endothelium and of cells The former is manifested by a disturbance in the distribution of fluid the latter by abnormal distribution of electrolytes Both these disturbances may result also from the action of any agents which increase the permeability of endothelium and of cells respectively

Gamble points out that the function of the kidney is not limited to excretion, it is the outstanding organ regulating and controlling the concentration of the extra-cellular fluid The kidneys cannot or will not filter fluid from blood which is abnormally concentrated (Marriott) nor can they function adequately when arterial blood pressure is low Renal dysfunction as related to disturbed fluid balance is discussed in Chapter XV

"Blood volume regularly is a question of balance between the fluids within the vessels and in the tissues When conditions arise which tend to lower or raise the volume of blood counterforces come into play which restore the normal level When circulatory fluid is lost the vessels replenish themselves from the extra vascular spaces. On the other hand any tendency for the blood volume to rise is met by a discharge of the excess fluid into the tissues or along the excretory routes So a balance is struck and in health the blood volume is maintained remarkably constant." (Best and Taylor p. 26.)

The maintenance of a constant composition of the interstitial fluid is essential to normal metabolism and normal function of the cells This is only one phase of a highly complex and exceedingly delicate mechanism Gamble holds that such terms as water metabolism salt metabolism acidosis alkalosis dehydration and

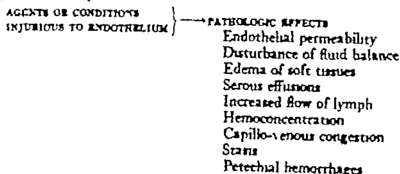
disorder prevents the absorption of fluid from the tissues, upsets the mechanism for preserving normal blood volume and concentration, and deranges other functions

CAPILLARY PATHOLOGY

The capillaries are not only delicately responsive to metabolites and to anoxia but they are highly sensitive to other influences as well They are susceptible to light, temperature, H ion concentration, and to a wide variety of organic and inorganic substances. In response to such agents the capillaries dilate, lose their normal tonus and the walls become abnormally permeable to colloidal substances Landis states that any type of injury to capillary endothelium increases its permeability to blood plasma. This is followed by the escape of fluid from the blood into the tissue spaces and by a corresponding increase in the flow of lymph from that area. When he obstructed an artery by pressure for three minutes the lack of oxygen thus produced caused a fourfold increase in the permeability of the capillaries in the field supplied by that artery Various chemical agents injected into the blood caused a sevenfold increase in endothelial permeability

The investigations of Krogh demonstrated that "capillary poisons, i e, those agents which produce injury to endothelium cause relaxation and dilatation of those minute vessels Capillaries so affected not only are dilated and their walls abnormally permeable to plasma they have lost their normal tonus and do not respond to nerve impulses nor to physiologic agents which cause normal capillaries to contract The endothelium of the venules is affected in the same way as that of the capillaries. Stasis of circulation developed promptly in atonic capillaries and venules and this condition became irreversible unless relieved within a few minutes.

The pathologic effects of injury to endothelium may be shown diagrammatically as follows



When the endothelium is injured by any agent or condition, it allows plasma to escape into the tissue spaces thus producing edema and, oftentimes, serous effusions The corpuscles become closely packed in the dilated capillaries and venules, and circulatory stasis results Stasis of the circulation is the surest sign of increased endothelial permeability (Landis), at the same time there occurs an increase in the number of corpuscles per unit volume of blood If the area of capillary atony is local, the hemoconcentration may be limited to that field If capillary atony has occurred in extensive visceral areas, the corpuscular content of the blood in the systemic circulation is increased in a degree proportional to the total loss of plasma from the blood, this, in advanced stages, is accompanied by a decline in the arterial blood pressure

As a result of capillary atony, there is a decrease in both the *actual* and the *effective* blood volume The leakage of plasma into the tissue spaces and cavities reduces the actual blood volume and produces hemoconcentration The sequestration of blood by stasis in dilated capillaries and venules reduces the return flow of venous blood to the heart This lowers the venous blood pressure and decreases the amount of blood actually in circulation—the effective blood volume—which reduction tends to lower the efficiency of the circulation by producing a disparity between the volume of blood and the volume capacity of the vascular system That disparity results in part from the reduced blood volume and in part from increased volume capacity incident to dilatation of the vascular stream bed

Compensation.—When the volume of blood is lowered and the pressure tends to decline, physiologic reactions are excited which tend to compensate the deficiency Impulses, probably originating in the carotid sinus, activate the sympatho-adrenal system which mobilizes the resources of the body for maintaining circulatory efficiency The discharge of adrenalin into the circulation stimulates the myocardium and mobilizes glucose into the blood from glycogen stored in the liver The volume capacity of the vascular system is reduced by constriction which is selective in action, favoring vital organs at the expense of peripheral parts The arteries are maximally contracted, the peripheral veins are collapsed and bloodless, and the spleen is reduced in size and in content of blood These effects reduce the volume capacity of the vascular system and maintain efficient cardiac function Under normal conditions the capillaries and venules may also be constricted, but when they have been affected deleteriously by

poisons toxins, irritants or by partial anoxia, the capillaries may become atonic and unresponsive to stimuli which cause normal capillaries to contract

Another phase of compensation tends to increase the volume of blood in circulation This includes the discharge of blood from reservoirs, such as the spleen, and the absorption of fluid from other sources. The latter is the chief means for restoring loss of blood volume It includes the fluid absorbed from tissues, resulting in their relative dehydration and that supplied by the gastro-intestinal route When moderate loss of blood has resulted from hemorrhage, the volume is restored rapidly by absorption, but when similar loss of volume occurs incident to endothelial damage, the mechanism of absorption is rendered ineffective Instead of increased blood volume by absorption, the blood continues to lose more fluid by leakage

So long as the compensation is effective, there is no ominous decline in the blood pressure but the latter is maintained at the expense of the volume flow of blood. Maximal arterial constriction may reduce the volume flow below an adequate physiologic level and may decrease seriously the delivery of oxygen to the tissues Capillary endothelium is delicately sensitive to lack of oxygen When tissue anoxia develops, the capillaries become atonic and abnormally permeable, thereby augmenting the previous capillary damage This effect gives the circulatory disturbance a self perpetuating quality which operates as a vicious circle (see p 53)

When the physiologic reactions described no longer compensate the disparity between the blood volume and the volume capacity of the vascular bed the circulation becomes obviously inefficient, the blood pressure declines progressively and the clinical syndrome of circulatory collapse or shock is manifested

Summary —Physiologists have supplied information concerning the enormously important functions performed by capillary endothelium. When that information is collected and summarized it appears that no tissue or organ serves more diverse and essential rôles than those of endothelium.

It seems that the blood serves its functions of distributing needed substances to the ultimate consumers—the cells—and of collecting and eliminating wastes such as urea CO_2 and others only when the blood is thinly spread upon a diffusion membrane—the endothelium The absorption of oxygen fluids, hormonal and other substances and the elimination of excess water and heat

likewise are performed in the capillaries by diffusion through endothelium

Substances discharged from cells, either as a result of functional activity or of any kind of injury, cause the adjacent capillaries to dilate and to become more permeable This is a local physiologic effect resulting in functional or inflammatory hyperemia respectively

The action of osmosis, and the maintenance of fluid balance between the blood and the tissues, are absolutely conditioned upon the presence of a normal semipermeable membrane—the endothelium—between those compartments

Agents or conditions which affect endothelium deleteriously alter its quality of semipermeability The resulting functional disturbances depend on the extent and degree of this alteration If extensive and severe, any or all of the processes mentioned may be retarded, interrupted or abolished Abnormal endothelial permeability upsets the mechanism of fluid balance and of absorption, by which the blood is maintained at a composition and volume within physiologic limits, as a result, the blood volume decreases and its concentration increases Disturbance of renal function results, for the process of filtration through the glomerular endothelium is lowered progressively with hemoconcentration

A wide variety of substances, including chemical poisons, extracts of normal tissues, products of protein cleavage, venoms and poisons of animal and bacterial origin, and others, have the property of injuring endothelium If such substances gain access to the circulation they may cause capillary permeability, dilatation and loss of tone in extensive areas That effect may derange the functions described, may upset seriously the mechanism of fluid balance and may disturb the systemic circulation by creating a disparity between the volume of blood and the volume capacity of the vascular bed The combination of these effects results in the complex syndrome of shock.

Deficiency of knowledge concerning capillary reactions and endothelial function, as summarized in this chapter, was one major hindrance to a comprehension of disturbances of fluid balance and of other phenomena of shock Other important hindrances to an understanding of shock will be discussed subsequently

CHAPTER II

CHARACTERISTIC FEATURES OF SHOCK

Terminology —There are valid objections to the term *shock* because of its common use in vague and indefinite senses, but attempts to substitute a more exact word have not met with success Cannon suggested that the term *exemia* should be adopted, since it implies one of the major phenomena of shock—the depleted total blood volume Failure to adopt this or some other specific term illustrates the difficulty of supplanting a word which has become widely used I have discussed the occurrence of shock under *circulatory failure of capillary origin* More recently Blalock has spoken of it as *peripheral circulatory failure* This is the condition usually referred to by physicians as shock It seems expedient to define that term in items of its physiologic attributes (see p 44) and to use the word accordingly

Much effort and ink have been expended in attempted differentiations between *shock* and *collapse* Let it be emphasized that the circulatory deficiency which will be defined as shock, occurs in varying degrees and develops with varying rapidity Differentiations based upon these variations are like distinctions between breeze and wind. When collapse presents as it usually does the features embodied in the definition for shock the terms may be regarded as interchangeable

Several terms have been used to denote concentration of the blood We have employed the word *hemoconcentration* as meaning an increase in the ratio of red corpuscles to plasma per unit volume of blood or in other words a numerical increase in the erythrocytic count. Often this is accompanied by a decrease in the concentration of proteins in the plasma. Let it be emphasized that hemoconcentration should be used only to denote a *rapid increase* the term should not be applied to *persistent erythrocytosis* associated with chronic passive congestion chronic CO poisoning, erythremia and the like

The terms *anhydremia* and *dehydration* have been employed by some authors as if synonymous with hemoconcentration. There is no apparent objection to *anhydremia* when so used but since *dehydration* is applied also to tissues its use as denoting concentration of the blood creates confusion Usually hemoconcentration is accompanied by an increase of water in the tissues, conversely

the tissues frequently are dehydrated while the water content of the blood remains unchanged To avoid this confusion it seems logical to use *dehydration* as referring *only* to the tissues, and to denote loss of fluid from the blood by *hemoconcentration* or by *anhydremia*

Clinical Features —The clinical signs of shock are well known The patient is weak and profoundly depressed Metabolic and functional activities are low The skin is pale and moist with cold perspiration The eyes are sunken, the features are drawn and anxious in expression producing the classical "Hippocratic facies" Normal tissue turgor is absent, the flesh has a lifeless doughy feel, and the superficial veins are collapsed and bloodless There is constant thirst but efforts to relieve it are ineffectual because of persistent vomiting Urination is decreased, the urine is concentrated and contains albumin, red cells, granular débris and other abnormal substances Often there is diarrhea and the feces may contain mucus and traces of blood The respirations are shallow and are interspersed with deep sighs The pulse is rapid and weak, it may be imperceptible in the peripheral arteries and, in late stages, the blood pressure declines progressively Temperature changes are variable After surgical operations or severe trauma, low temperatures are common but after burns and in shock from certain other causes the temperature may be increased The patient is restless, "picking at the bed clothes" and may become delirious As the condition progresses there are apathy, loss of sensitivity and of reflexes Death is preceded by stupor or coma

A highly significant feature is the presence of small brown flecks, often called "*coffee grounds vomitus*," in the fluid vomited by patients in shock These flecks give a positive response to phenylhydrazine and to other tests for hemoglobin This phenomenon has puzzled clinicians, pathologists and others for many years The flecks are now interpreted as derived from capillary hemorrhages in the gastric mucosa and as indicative of endothelial damage They are therefore related to the pathologic physiology of shock

PHYSIOLOGIC DISTURBANCES

The clinical syndrome described is accompanied by a characteristic group of variations from physiologic constants These will be considered in related groups

Cardiovascular —A marked *decline in the arterial blood pressure* has been overemphasized as a cardinal feature Meltzer (1908)

stressed the fact that low blood pressure is not regularly present Gray and Parsons (1912) stated that *increased* blood pressure occurred in the first stage and that occasionally other signs of shock were manifested while the blood pressure was at its highest recorded point Mann (1914) was impressed by the fact that animals often might show all the signs of shock except a marked decline in the blood pressure Cowell (1919) observed that no immediate fall in arterial pressure occurred in severely wounded men, but moderate increases were common in such cases the decline in blood pressure occurred several hours later Blalock (1927) stated that the blood pressure is an inadequate guide to the state of the circulation in incipient shock Cope (1935) corroborated the findings of Gray and Parsons, he stated that hemoconcentration and other signs indicated shock more reliably than the blood pressure Wilson and his associates (1937–38) observed an *increase* in the blood pressure in 35 out of 40 cases of severe burns seen within two hours after the accident. Fishberg (1940) states that the blood pressure may remain normal for hours or even days in otherwise typical cases of shock

There is no doubt that a marked and progressive decline in the arterial pressure occurs in the late stages of shock It appears that so long as the mechanism of compensation is adequate there is no marked prolonged hypotension, when the latter develops, it indicates ineffective compensation or decompensation

Changes in the rate and quality of the pulse vary with the stage and degree of shock The rate is not markedly increased in incipient shock, often the pulse is slow and strong It increases in rate as the blood pressure declines and when decompensation occurs it becomes very rapid, thread like and of low volume.

The pulse pressure likewise is inconstant McKesson (1916) reviewed the findings in 5000 surgical operations He recorded a decreased pulse pressure as a feature of shock This was corroborated by Moreau and Benhamou (1918) However, Archibald and McLean reported the observation on severely wounded soldiers that an *increased* pulse pressure was characteristic of severe shock in an advanced stage

Many observations indicate that the venous pressure is very low in shock Cannon described the superficial veins as collapsed or contracted These filled slowly when a tourniquet was applied to the limb Eppinger emphasized this feature as a distinguishing characteristic of shock Many observers have noted the difficulty of securing blood by venipuncture from patients in shock and

others have found it necessary to open the tissue and expose a vein when giving fluid intravenously in treatment Fishberg measured the venous blood pressure in many cases of shock, he found this markedly reduced, often to 1 or 2 cm H_2O

On the other hand, Scudder has reported *increased* venous pressure in shock Such a finding is not in keeping with clinical evidence nor with the low peripheral circulation which is a cardinal feature of shock One recalls that other conditions, as cardiac failure or fat embolism, may simulate shock closely and that increased venous pressure is characteristic of them Is it possible that some observations on patients in those conditions have been interpreted as applying to shock?

Blood Volume —Fischer (1870–75) commented on the disappearance of blood from the circulation during shock "Where then is the entire blood volume? The heart contains no blood and the patients are pale as marble even when little or no blood loss resulted from the wound *Where then is the blood hiding?*" Henderson (1910) noted a decrease in the total blood volume, in the cardiac output and in the volume flow of arterial blood Mann (1914) noted a marked decrease in the volume of circulating blood and attributed the signs of shock to it He showed this was beyond the control of the vasomotor system, that it was peripheral rather than central in origin, but he was unable to show the mechanism of the "lost blood "

Robertson and Bock demonstrated a reduced blood volume in cases of shock resulting from wounds Keith made determinations of blood volume in wounded soldiers and found that the reduced volume paralleled closely the severity of shock When the blood volume was reduced by 25 per cent, grave symptoms appeared, when it was reduced 35 per cent, the condition became critical The reduction in volume was shown to be due to loss of plasma and was accompanied by corresponding hemoconcentration Dale and associates verified these findings in shock produced by injecting histamine Gasser, Erlanger and Meek, also many others, have confirmed these observations Cannon emphasized the "problem of the lost blood" as the chief enigma of shock and predicted that the explanation for this phenomenon would clarify the mechanism and origin of this condition Meek wrote "Shock is not the state which results from a fall in blood pressure It is the state which results from a decrease in the effective circulatory volume " There is no disagreement among writers concerning the *fact* of

reduced blood volume, but there has not been agreement concerning the *mechanism* of its development

Volume Flow —Henderson demonstrated in experimental shock that the cardiac output was markedly reduced before any decline occurred in the arterial pressure He criticized severely the view that the latter is the essential phenomenon of shock In his opinion, the central feature is the diminished venous pressure which causes a decreased return flow of blood to the heart This lowers the cardiac minute volume output and thereby results in low arterial pressure Gesell showed that a reduction of 10 per cent in the blood volume may cause a reduction of 60 per cent in the volume flow of blood Burch and Harrison found that the cardiac output declined by 40 to 50 per cent before arterial blood pressure fell This occurred both in shock resulting from trauma and from burns Wiggers stated "A decreased venous pressure and the consequent reduction in the minute output is the predominant factor in the pronounced fall of arterial pressure during the progressive stage of shock Dale and Laidlaw stated "The systolic output from the heart fails because the diastolic filling is inadequate." Eppinger concluded that the central factors in the hemodynamics of shock from all causes are the same a reduction in the volume of blood and in the amount returned to the heart. The latter feature explains the diminished cardiac output and volume flow It must be remembered that the heart is a force pump not a suction pump, it cannot draw blood to itself out of the tissues but can only pump the blood which is returned to it It has been shown that the heart decreases in size as shock develops, thus adapting itself to the decreased return flow of blood by decreasing its volume output

The decreased flow of blood through peripheral arteries is a prominent clinical feature The pulse in superficial arteries is small and thread-like or it may be imperceptible even when the heart is beating vigorously Surgeons frequently have commented on the fact that little or no bleeding may occur when arteries of medium size are severed in operations on subjects who are in shock These observations indicate that the arterial volume flow may be reduced almost to extinction when shock is well advanced The maximal arterial vasoconstriction which is one of the chief factors in this is a part of the mechanism of compensation described in Chapter I

Freeman Shaw and Snyder devised a method for determining the volume flow of blood clinically Their report indicates that,

when the circulation is becoming inefficient, the deficiency is compensated by vasoconstriction of the arteries This maintains the blood pressure at adequate levels but the compensation is at the expense of volume flow This may be reduced to a small percentage of the normal, which entails a corresponding reduction in the arterial circulation, before there is any notable decline in the blood pressure

Baldes, Herrick, Essex and Mann made observations on the volume flow of blood in peripheral vessels by means of a thermo-stromuhr When shock was induced in dogs by intestinal manipu-

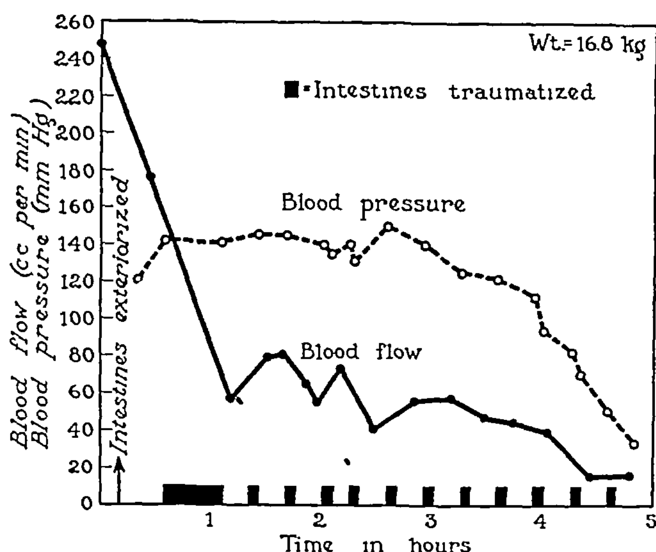


CHART 1 —Results of a typical experiment in which shock was produced by manipulation of the intestines (Baldes, Herrick, Essex and Mann, courtesy of Am Heart Jour)

Blood flow decreased 75 per cent but blood pressure rose and remained above 120 for four hours

lation, the flow of blood in the femoral artery declined immediately and reached a very low level several hours before the arterial blood pressure declined (see Chart 1)

Hematology —Many writers (Hunter, 1890, Sherrington and Copeman, 1893, Cobbett, 1897, King, 1902, Vale, 1904, Crile, 1909, Henderson, 1910, Mann, 1914) noted increased concentration of the blood during surgical or experimental shock During World War I this phenomenon was observed repeatedly in wounded soldiers

Cannon, Frazer and Hooper made erythrocytic counts, hematocrit readings and hemoglobin determinations in a series of cases of

hemorrhage and of wound shock in which little blood had been lost. They found that hemorrhage was followed by hemodilution which tended to be proportionate to the amount of blood lost. This was noted also in those who had served as donors for transfusion. Examinations of blood in cases of shock, accompanied by insignificant hemorrhage, showed hemoconcentration. Counts of red cells ranged from 6,000,000 in mild cases to 9,000,000 in severe cases. They stated that the first noteworthy feature in severe traumatic shock is a marked increase in the count of red cells. They attributed this to stasis of blood in capillary areas accompanied by transudation of plasma into the tissue spaces, with resulting concentration of the corpuscular elements.

Bazett found red cell counts and hemoglobin determinations valuable as indicating whether shock or hemorrhage was present and in estimating the condition of the patient and the degree of the operative risk. Robertson and Bock confirmed the findings of Cannon *et al*, of Bazett and of Keith. They found hemoconcentration in cases of shock and hemodilution after hemorrhage and made use of this in determining whether shock or hemorrhage was the dominant feature in the condition of severely wounded soldiers.

Hemoconcentration has a significance more grave than is commonly apprehended for it indicates with certainty that the mechanism of fluid balance is seriously disturbed. A further consideration of the occurrence of hemoconcentration and its usefulness in diagnosis, will be found in Part II, Chapters XX and XXI.

The blood shows regularly a group of changes other than hemoconcentration. The behavior of the leukocytes varies with the stage and the intensity of the condition. In early stages and in sublethal degrees of shock there is marked leukocytosis while in advanced stages and in shock of severe degree there is leukopenia. This is illustrated by the effects of histamine. Dale and his associates noted leukopenia regularly after injections of *lethal* doses of histamine in cats. Lieber and I found that *small* doses of histamine were followed by moderate leukocytosis in cats, monkeys and in human subjects. A few similar observations have been reported by others.

Cannon reported the presence of leukocytosis ranging from 30 000 to 50 000 after wounds. Counts ranging between 25 000 and 35 000 were found within two hours after the injury. The leukocytosis was transient and usually disappeared within forty eight hours. It occurred too early and subsided too rapidly to

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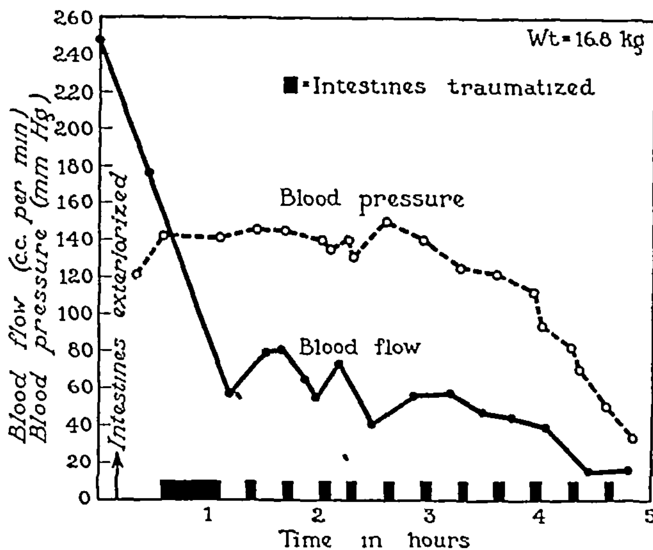


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has been explained as the result of increased mobilization of glucose from the liver, incident to increased activity of the sympatho-adrenal system The mechanism which tends to compensate circulatory deficiency causes an increased discharge of epinephrin into the circulation The mobilization of glucose is one of the physiologic effects of epinephrin Low metabolism resulting from decreased oxidation also tends to cause an accumulation of glucose in the blood (Aub and Wu)

The consumption of oxygen, the basal metabolic rate, declines progressively during clinical and experimental shock Aub found that the basal metabolic rate returned promptly to normal when recovery resulted from transfusions of blood

Flow of Lymph.—Many substances, when given by injection, will produce shock in experimental animals Examples of these are peptone, extracts of shell-fish and of other marine animals, extracts of liver and of other tissues, bile and cholic salts, tuberculin and other bacterial substances, foreign proteins in sensitized animals, histamine and the like The effect of these substances upon the circulation by causing damage to endothelium and the increased flow of lymph which results, were discussed in Chapter I Circulatory failure caused directly by anoxia, as in asphyxia and in CO poisoning, is likewise accompanied by an increased flow of lymph The same occurs also during anaphylaxis (Drinker and Field, pp 149–159)

Mann (1914) observed an increase in the flow of lymph from the thoracic duct beginning at the onset of shock Eppinger noted an increase both in the volume of lymph and in its protein content during shock produced by injections of histamine and of peptone On the other hand, hemorrhages promptly reduced the flow of lymph and its protein content to about one-third of that recorded before the hemorrhage Maurer cannulated the cervical lymph vessels of 9 dogs and then limited their respiratory oxygen In each, the flow of lymph was increased in volumes ranging from 1 2 to 4 8 times the normal The passage of protein from the blood capillaries to the lymph, calculated in milligrams per minute, increased correspondingly Acacia injected intravenously regularly appeared in the lymph These observations were believed to indicate that low blood oxygen and increased CO_2 result in increased capillary permeability with loss of fluid and protein from the circulating blood McCarrell and Drinker cannulated the cervical lymph vessels and then maintained the blood pressures between 40 and 60 mm Hg by injections of small amounts of

histamine "A few minutes after the onset of the low arterial pressure the cervical lymph flow increased, and peaks were quickly reached that were 1 1 to 4 9 times the normal level" The percentage of protein in the lymph decreased but the flow was so voluminous that the protein in milligrams per minute was markedly increased

In one group of 3 dogs we cannulated the thoracic duct and then induced shock by implanting muscle pulp into the peritoneal cavity (see pp 122–127) Soon the rate of lymph flow increased and within ninety minutes hemoconcentration was noted. These effects progressed in degree and the concentration of the blood continued until death, which occurred eight to ten hours later As the dogs became moribund the rate of lymph flow declined The lymph at first was grayish in color then yellowish pink, then bright red from a progressive increase in its content of erythrocytes The readiness with which the lymph formed clots indicated an increased content of fibrinogen

Summary —The use of the terms *hemoconcentration* or *anhydremia* is recommended to denote loss of fluid from the blood To avoid confusion, the term *dehydration* should be used only as referring to a decreased fluid content of the tissues

The signs which indicate the fully developed clinical syndrome of shock are too well known to justify repetition That syndrome is accompanied by a group of characteristic deviations from normal physiologic conditions

The blood pressure often rises and it is well maintained during the early stages of shock a progressive decline occurring in the later stage indicates failure of the mechanism of compensation and the imminence of death The pulse pressure usually is reduced, perhaps because of decreased peripheral resistance to blood flow A low venous pressure usually precedes the decline in arterial pressure

Both the actual and the effective blood volume is reduced and the degree of this reduction is proportionate to the degree of the circulatory deficiency

The volume flow of blood through peripheral parts is markedly reduced long before an ominous decline in the arterial pressure occurs. A decrease in the venous return flow decreases correspondingly the cardiac output. This is counteracted by maximal vasoconstriction but the latter reduces markedly the volume flow of blood in the tissues

An increased flow of lymph occurs early and apparently is due

to abnormal endothelial permeability Obviously this is related to disturbed fluid balance

Hemoconcentration occurs early and tends to progress in a degree corresponding to the degree of shock Hemoconcentration indicates abnormal permeability of endothelium and the consequent disturbance of fluid balance

Leukocytosis in early stages is followed by leukopenia as the circulation becomes ineffective A marked decrease in the coagulability of the blood occurs in shock resulting from various causes

The oxygen content of the blood declines and the basal metabolic rate is reduced both by the low oxygen content and by the decreased volume flow of blood through the tissues There is an increase in the blood glucose, due partly to the low metabolism and partly to an increased mobilization from the glycogen in the liver

There is a progressive decline in the reserve alkalinity of the blood Several authors attribute this to deficient oxygenation

Changes in the electrolytic concentrations of the blood include low chloride, sodium and carbonate content and an increase in potassium, magnesium and in the lactic, phosphoric and sulphuric acid radicles The mechanism of these changes is explained under *cell permeability* in the following chapter

CHAPTER III

OTHER CHARACTERISTICS DEFINITION

A NUMBER of items in the pathologic physiology of shock have been discussed Most of these have been described and their occurrence verified repeatedly by others Two additional features have not been analyzed as related to shock although they have been observed by previous writers For this reason and because of their fundamental importance in that syndrome, they merit detailed consideration

CELL PERMEABILITY

In the discussion on *fluid balance* it was said that living tissues present three "compartments" or "phases"—vascular, interstitial and intra-cellular—and that the chemical composition of the fluids in them differs markedly These differences pertain to proteins electrolytes and water The maintenance of the normal difference between the blood and the tissue fluid is a function of endothelium consequently abnormal permeability of capillary walls disturbs osmosis and fluid balance. Cytoplasmic fluid differs markedly from interstitial fluid in its content of protein and electrolytes The maintenance of this differential is a function of living protoplasm hence variations in this function of living cells will create disturbances of electrolytic equilibrium with resulting chemical variations in the extra-cellular fluids

Students of cell physiology (Lucké and McCutcheon for review) have shown that the outer protoplasmic surface of each living cell functions as a semipermeable membrane and that, by virtue of this each cell behaves as an osmotic unit. Also that transfer of water between the cell and the extra-cellular fluid depends chiefly on differences in osmotic pressure in accordance with the laws of osmosis and diffusion Eppinger stated that poisons which cause capillary permeability also affect deleteriously the permeability of the cells. Almost immediately there are variations in the normal chemical differences between the tissues and the blood as an interchange of anions and kations occurs. He believed this indicated that the cells had lost something of their vital function and that they were approaching death The severity of the injury determined whether the cells may recover It is known that tissue

anoxia will produce a similar variation from normal ionic concentrations

Some property possessed by living protoplasm maintains chemical concentrations within the cell, differing markedly from those of the external fluid This property is reduced by any kind of injury to the cell and is lost entirely as the cell dies Loss of this property allows substances to pass freely from the region of higher concentrations to that of the lower, thus equalizing the differences in composition between the intra- and extra-cellular fluids (see Fig 2)

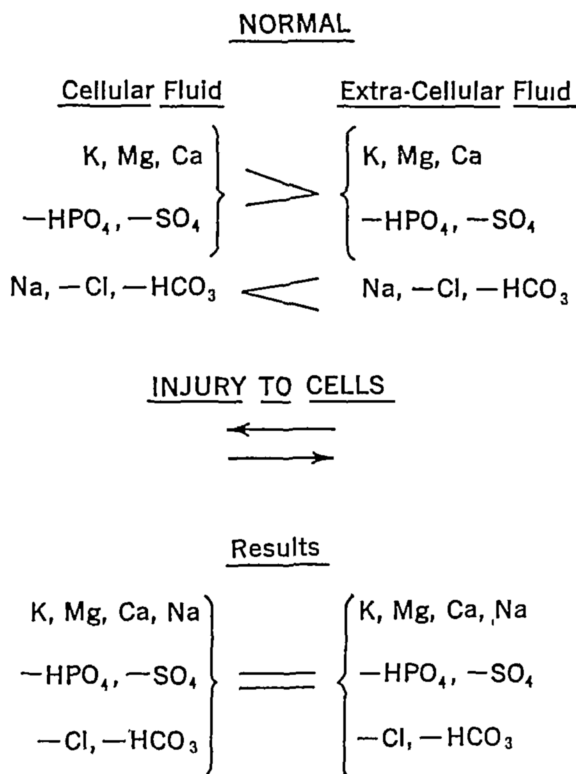


FIG 2 —The upper part of this diagram shows important differences in the electrolytic concentrations between the cellular and extra-cellular fluids Injury to the cells disturbs electrolytic balance, allowing the ions to move from the regions of the higher to those of the lower concentrations This process causes characteristic chemical alterations in the blood and in the tissues

It has been shown (Gamble) that cytoplasm contains a higher concentration of potassium, calcium and magnesium bases, and of the $-SO_4$ and $-HPO_4$ acid radicles, while the interstitial fluid is higher in sodium and in the $-Cl$ and $-HCO_3$ ions Many authors have noted, and Scudder has emphasized this point, that the plasma and interstitial fluids lose sodium, chlorides and car-

bonates and gain in potassium, calcium and magnesium during the development of shock. These changes indicate that cell surfaces have become permeable and that normal differences in composition are no longer maintained Scudder suggested that the high potassium content of the extra-cellular fluids *causes* injury to the cells and hence contributes to the development of shock. However he stated "an increase in the specific gravity of the peripheral blood preceded by hours, in some instances by days, the ultimate hyperpotassemia" Hence it appears more probable that the cellular injury is *the effect* of the shock producing agent, with resulting shifts in ionic concentrations as described The fact that hemoconcentration occurs early, and the chemical changes later, supports the view that the latter are effects rather than causes.

The ratio of cellular to extra-cellular potassium is about 20 1 The extra-cellular fluids have been estimated as 15 per cent of the body weight A simple computation, on the basis of these figures, indicates that complete equalization in the ionic concentrations would result in raising the potassium content of the extra-cellular fluids to approximately 18 times its normal level None of the published data, on chemical alterations in the blood during shock, have shown such a high potassium content as this It is evident that this maximal level could only be reached by *complete* equalization of the chemical concentrations, which condition probably would occur at or after death Cellular injury tends to allow equalization in the concentration of other ions as well.

It is recalled that any type of injury to endothelium, no matter how it is produced, increases its permeability to such a degree that even colloids escape through the endothelial membrane This abnormal *endothelial* permeability disturbs seriously the mechanism of fluid balance, as discussed in the preceding chapter Likewise any type of injury to *cells* increases the permeability of their walls. The same agents which disturb the circulation and the mechanism of water balance by injuring the endothelium may likewise disturb vital chemical concentrations by increasing *cellular* permeability The former effect results in shock accompanied by hemoconcentration, the latter effects account for several of the accompanying alterations in the composition of the blood plasma and tissue fluids.

Chemical changes are highly significant as related to cellular injury and many writers have emphasized the gravity of *hypochloremia* as a complication in various clinical disorders. It

appears that the full significance of this condition has not been comprehended, though the seriousness of the disturbed physiology is unquestionable. The movement of sodium chloride from the blood into the tissues is associated with that of other ions, both acid and basic, in the opposite direction. It seems probable that increased cellular permeability, which allows such shifts to occur, is the underlying cause and that the hypochloremia and other associated chemical variations are results. These shifts in ionic concentrations are of grave importance because they indicate serious injury to tissue cells.

DISTURBANCE OF RENAL FUNCTION

Few features of shock have deserved more and received less attention than has this. Early clinical descriptions of the symptoms relate that the urine is scanty or suppressed, that it is concentrated, dark in color, has a high specific gravity and contains various abnormal chemical and morphologic constituents. These observations have been repeated consistently until the present time, yet their origin and significance have not been explained, neither have they led to penetrating investigations.

Likewise examinations of the blood have consistently shown evidence of renal excretory deficiency as an aftermath of surgical operations, trauma, burns, intestinal obstruction and of other conditions leading to shock. Yet observers have been so intent in seeking the cause of the circulatory deficiency that they have done little more than record the fact that excretion of nitrogenous wastes is seriously impaired.

An increase in the non-protein nitrogen of the blood is an outstanding feature in shock from various causes. This was reported in traumatic shock (Duval and Grigaut, Cannon), in experimental shock (Aub and Wu, Beard and Blalock), in anaphylactic shock (Jobling and Petersen, Wells, Segall), after burns (Underhill, Davidson, Wilson), in intestinal obstruction (Whipple and associates, Draper, McVicar, Guest and Andrus, Scudder), after injections of histamine (Hashimoto), in peptone and proteose poisoning (Whipple and Van Slyke), in intoxications and infections (Cooke and Whipple), in acute adrenal cortical insufficiency (Banting and Gairns, Rogoff and Stewart, Swingle and associates) and in *x*-ray sickness (Hall, Whipple, Warren).

Beginning about twenty-five years ago, Whipple and his associates (Stone, Bernheim, Cooke, Rodenbaugh, Foster, Hall, Van

Slyke, Smith Belt, Warren) produced fatal shock-like circulatory disturbances in dogs and noted several highly significant physiologic disturbances. These occurred after various types of intestinal obstruction, after injections of proteoses, sublethal poisoning with phosphorus, with chloroform and with hydrazine, extensive sterile abscesses, staphylococcic infections, pleuritis, pancreatitis and other conditions. They noted low blood pressure, hemoconcentration as indicated by hematocrit readings, and decreased renal elimination in all such experiments There was a marked retention of nitrogen wastes—3 to 10 times the normal level—which they interpreted as resulting from severe injury to tissue cells. The rapid piling up of nitrogen in the blood suggested a rapid breakdown of protein substances and retarded renal elimination "The animals will die in twenty four to thirty-six hours in a characteristic condition of surgical shock "

Whipple and Van Slyke (1918) noticed an increase of 40 per cent or more in the non protein nitrogen of the blood of dogs after injections of proteoses This increase consisted chiefly of urea but included amino and peptid nitrogen as well To them this indicated abnormally rapid auto-digestion of the tissue proteins. As in previous studies, a marked concentration of the blood, shown by hematocrit readings, accompanied the condition Later (1925) Whipple Smith and Belt produced cellular injury by plasmapheresis When the plasma proteins were reduced to an abnormally low level the animals showed signs like those of fatal anaphylaxis They stated that the picture corresponded with that of surgical shock and with that of fatal intoxication by intestinal obstruction The autopsy findings showed uniformly the same pattern later described for shock (see Chapter XI) and the authors commented on the similarity of their results to those of Erlanger and associates in shock produced by other means The non protein nitrogen was sharply elevated in all such cases—a feature previously noted by them in experiments on intestinal obstruction They concluded ' this is further evidence for actual cell injury as an essential part of the clinical complex named 'shock' "

Duval and Grigaut (1918) noted an increase in the non-protein nitrogen and in the residual nitrogen in the blood of severely wounded soldiers. This seemed proportionate to the degree of shock rather than to the severity of the wounds Richet and Flament in the same year reported on deficient renal function under the same conditions

Reimann and Hartman (1919) made chemical studies of the

blood before and after surgical operations in about 90 unselected cases The blood urea and non-protein nitrogen were increased in every case This indicated either retention or increased production of nitrogenous wastes Aub and Wu (1920) found the urea and creatin sharply elevated as shock developed "The marked rise in creatin is direct evidence of the presence in the blood of products of muscle necrosis and is therefore suggestive evidence of the theory of the chemical cause of traumatic shock "

Peters and Van Slyke state that serious grades of azotemia occur in the first five days after extensive surgical operations in patients having no evidence of renal disease "It is probable that toxic destruction of protein, resulting from trauma, shock, and the conditions which compelled the operation together with dehydration were responsible "

Derow's discussion of this syndrome substantiates those previously mentioned He noted marked oliguria in the first few days after major surgical procedures The urine was concentrated and its specific gravity was above normal, while the non-protein nitrogen of the blood was sharply elevated "In many of these patients circulatory collapse may play a major rôle in the genesis of the oliguria and the resulting azotemia Postoperative rises in the blood non-protein nitrogen attributed to general anesthesia are more probably due to toxic destruction of protein resulting from trauma, shock and the condition which required operation " Lurje's report is of the same character, he found a high non-protein nitrogen after operation in 8 cases in which signs of shock developed This lasted until the period of shock was over in those who recovered

Lambret and Driessens made an extended report and analysis of this feature, combining experimental data with observations before and after various surgical procedures They described a complex tissue-fluid syndrome characterized by the following distinctive features oligemia, preceded by transient hypertension and followed by moderate hypotension, a marked decrease in the reserve alkalinity, hypochloremia, hyperazotemia, increase in platelets, hyperglycemia, leukocytosis and mononucleosis, and accelerated sedimentation rate

The hyperazotemia was regarded as a most important item in this postoperative syndrome There was a rapid increase in the urea and in "toxic polypeptids " This elevation was variable but often amounted to 5 times the normal Mild degrees of this subsided in twenty-four to thirty-six hours, some persisted for

several days and others progressed, reaching 250 to 330 mg per cent

The authors explained this high level of nitrogenous wastes as the result of parenteral digestion of damaged tissue The entire postoperative syndrome depended on several factors metabolism, anesthesia, neurologic and vascular disturbances, oligemia, con tusions and cellular destruction They regarded tissue trauma as the most important, and the other factors as minor In their opinion trauma followed by resorption of products of tissue digestion is a factor relating the postoperative syndrome to trau matic shock, the effects of burns, destruction of tissues by x ray, and the like

Changes of the same type regularly occur after extensive burns of the skin Robertson and Boyd reported an increase of from 40 to 50 per cent in the blood non protein nitrogen of rabbits after burns. Moorhead and Killian found an elevation of the non protein nitrogen and an unusually high amino-nitrogen in severely burned patients Pack stated that the erythrocytic count increased by 2 to 4 million and that albumin appears in the urine almost immediately after severe burns The urine is decreased in amount, smoky in color and has a high specific gravity He assigned the retention of nitrogenous wastes and the oliguria to impaired renal function and to the fact that concentrated blood has insufficient fluid to exert a hydremic stimulus on any kidney Also the ammonia nitrogen was increased and acetonuria occurred fre quently about the third day The sodium chloride of the blood varied inversely with the hemoglobin content, it was lowest in cases with the highest hemoconcentration Wilson and his asso- ciates confirmed the abnormal urinary finding previously men tioned both in a large series of clinical cases and in experimental burns in cats The urea and the non protein nitrogen were sharply increased both in the serum and in the whole blood. The literature on burns contains numerous similar reports on retention of wastes and abnormal urinary findings after burns. Lam has reviewed the reports which have appeared recently concerning the chemical pathology of burns He states that urinary changes have not received adequate attention. Oliguria, high specific gravity and albuminuria occur almost regularly Ketonuria, hemoglobinuria and bilirubinuria are evidence of the excess of those substances in the blood

Some striking observations on renal deficiency associated with shock are found in recent reports on ' crush injuries seen as air raid casualties in London (Bywater, Beall Belsey and Miles)

Many victims of bomb explosions were pinioned by limbs, caught in débris of wrecked houses, and were not released for many hours The first report is based on 4 cases, their condition on being rescued was apparently good except for swelling and contusions of the limb and an elevated hemoglobin content of the blood Later they manifested pallor, sweating, coldness and a decline in the arterial blood pressure This was restored and maintained by transfusions of plasma, serum or blood "Signs of renal damage soon appear and progress even though the crushed limb be amputated The urinary output initially small, owing perhaps to the severity of the shock, diminishes further The urine contains albumin and many dark brown or black granular casts " In some there were hyaline casts, red cell casts and erythrocytes Thirst and vomiting were incessant but the blood pressure was slightly elevated The blood urea and potassium became steadily higher and death occurred within a week

Complete necropsy data were not published Necrosis of muscles was found in the areas crushed, some liquefaction was seen microscopically The kidneys were enlarged, they showed severe degeneration of the proximal convoluted tubules, desquamated epithelial cells and darkly pigmented casts The glomeruli were not visibly abnormal but the capsular spaces contained albuminous material The authors commented that the course of events and the postmortem findings were like those resulting from transfusion with incompatible blood, but the patients had been benefited by the transfusions and had shown no untoward reactions The authors noted that necrosis of muscles was the one factor in common in these cases

When shock leads to death promptly, evidences of renal deficiency are not prominent, although oliguria is apparent and examination of the blood indicates the retention of nitrogenous wastes But when death is delayed several days, the renal functional deficiency is cumulative and may produce manifestions of uremia This feature is exemplified and discussed as *extrarenal uremia* in Chapter XV

DEFINITION OF SHOCK

Perhaps a majority of those who have written on shock have tried to define it, certainly numerous attempts are on record The definitions proposed are of two general forms those in which the author incorporated some theory of origin into the

definition, and those based upon clinical signs. Some represent combinations of these forms. A few illustrative examples follow
Shock is

> A species of functional concussion by which the influence of the brain over the organ of circulation is deranged or suspended (Travers, 1826)
>
> A depression of the vital powers, induced suddenly by external injury and essentially dependent on loss of innervation (Gross, 1872)
>
> A sudden check to the circulation brought about through the agency of the nervous system (Mansell Moullin, 1882)
>
> A lassitude or relaxation of the spinal marrow and of the medulla oblongata, produced by violence (Crile, 1899)
>
> A condition produced by exhaustion of the vasomotor centers and the resulting great fall in blood pressure (Mummery, 1905)
>
> The result of the depressive effects of traumatic toxemia (Quénu, 1918)
>
> The collapse of the circulation from overstimulation of the sympathetic nervous system (Tomb, 1937)
>
> Anoxemia which is the resultant of such factors as oligemia lowered blood pressure, diminished flow of blood and peripheral vasoconstriction (Davis, 1937)
>
> A state of depression of all the reflex arcs accompanied by circulatory depression (Devine, 1939)
>
> A progressive vasoconstrictive oligemic anoxia (Harkins, 1941)

Strictly speaking, these and others of their kind are epitomized theories of origin rather than definitions. Perhaps the true function of a definition is not to advance theories concerning the cause of a phenomenon but rather to state its attributes so precisely as to differentiate it from other phenomena which it may resemble It appears that definitions of the type illustrated do not serve this function

Another type of definition consists in stating one or more of the outstanding clinical features manifested by patients A medical dictionary (Stedman) defines shock as *a state of profound mental and physical depression consequent upon severe physical injury* A standard treatise on surgery (Rose and Carless) defines it as *a condition of depression of the vital activities of the body, associated with a marked and progressive fall in blood pressure resulting from injuries* These statements are too brief to distinguish the

condition from others, and they limit incorrectly its occurrence to the effects of injuries

Cannon avoided the difficulty of defining shock by giving two excellent clinical descriptions of patients in that condition Several definitions based upon a combination of clinical features might be quoted, Blalock's definition (1927) is cited as an example representative of these *Shock is used to denote a condition of acute circulatory failure characterized by prostration, apathy or stupor, tachycardia with feeble regular pulse and, in many instances, diminished blood pressure The temperature of the body is often subnormal Pallor and slight cyanosis are usually present*

It seems that definitions of this type approached their goal more closely, but clinical signs alone may not differentiate shock from other conditions For example, syncope, fright, hemorrhage, physical exhaustion, anesthesia, primary shock, cardiac failure and circulatory deficiency from diverse causes may produce a condition corresponding closely to the definitions given

It was thought that the existing confusion might be cleared somewhat if a definable entity could be segregated from the heterogeneous conditions which resemble shock Accordingly the accompanying physiologic disturbances were considered thoughtfully and a group of them was selected and proposed (1936) as a definition *Shock is a circulatory deficiency, not cardiac nor vasomotor in origin, characterized by decreased blood volume, decreased cardiac output (reduced volume flow) and by hemoconcentration* If amended in accordance with suggestions and criticisms received subsequently from others, this might read *Shock is a circulatory deficiency of peripheral origin, characterized by decreased blood volume, decreased cardiac output, reduced volume flow, and by progressive hemoconcentration* That statement seems to embody the same essentials and perhaps some will prefer it

Since proposing the first definition we have continued to examine this complex phenomenon, and our view of it now is perhaps more comprehensive If this view should be embodied in a definition, it would read

Shock is a disturbance of fluid balance resulting in a peripheral circulatory deficiency which is manifested by a decreased volume of blood, reduced volume flow, hemoconcentration, and by renal functional deficiency

This disturbance of fluid balance may originate from sundry and diverse causes, as will appear in the discussions which follow, but each of them effects, either primarily or secondarily, the permeability of endothelium

CHAPTER IV

ANOXIA AS RELATED TO SHOCK

A THOUGHTFUL consideration of the vascular dynamics of shock indicates that two major factors operate to produce it. One of these, *endothelial damage*, has been discussed. It was shown that various injurious agents may cause atony of the capillaries and thereby create a disparity between the volume of blood and the volume capacity of the vascular bed; also that abnormal permeability of endothelium disturbs fluid balance, allows leakage of fluid into the tissues, causes hemoconcentration and reduces the blood volume. These effects result in a decreased volume flow of blood in systemic areas. The latter tends toward a circulatory deficiency which, if sufficient in degree, reduces the delivery of oxygen to the tissues.

Lack of oxygen—*anoxia*[1]—is the second major factor in the mechanism of shock. Anoxia is of the highest importance, not only because it reduces metabolism and other vital activities but also *because lack of oxygen damages endothelium and increases its permeability*. As Haldane expressed it, this not only stops the machine, it wrecks the machinery.

Landis found that, after obstructing the blood supply to an area of tissue for only three minutes, the capillary endothelium in that area became 4 times as permeable as normally. Erlanger and associates reported that tissues showed capillary engorgement like that of acute inflammation, after the release of a temporary arterial obstruction. *Reactive hyperemia* resulting from temporary ischemia in living tissues, is a well known phenomenon, the engorgement is due chiefly to lack of oxygen causing dilatation of all capillary channels in the area of tissue affected. When circulation has been reëstablished and the oxygen deficit has been repaid, the capillaries may regain their tonus and the hyperemia subsides. Obstruction of the venous circulation has a similar effect. The passive hyperemia which results from a tourniquet applied about a limb involves the capillaries as well as the venous channels.

[1] The term *anoxia* literally means complete lack or absence of oxygen. In these chapters, the term is employed in a relative rather than literal sense. Brevity seems to justify the use of one word denoting *a decrease in the oxygen supply below physiologic limits*.

The obstructed circulation limits the oxygen supply and creates a deficit If anoxia from passive congestion is sufficiently prolonged and of marked degree, the endothelium becomes abnormally permeable and edema develops in the tissues Krogh showed that all the capillaries in an area of tissue temporarily deprived of blood, became dilated, permeable to the plasma and densely packed with corpuscles After fifteen minutes deprivation of oxygen, the condition of stasis became irreversible It was not relieved by reestablishing the arterial circulation From these examples one may deduce what a grave systemic circulatory disturbance may develop if extensive visceral areas should be deprived of an adequate supply of oxygen

A circulatory deficiency, having all the clinical and physiologic features of shock, may be produced by limiting the distribution of arterial blood either systemically or locally Instances of this will be described

Shock by Anoxia —The first experiments of this kind of which I have found record, were those of Janeway and Jackson They placed a loop of cord about the vena cava and, by exerting traction, retarded the circulation by reducing the venous flow until the arterial pressure declined to 30 or 40 mm Hg After two hours the loop was released and the circulation reestablished Shock developed following the release of the obstruction in these dogs

Erlanger and associates repeated the experiment of Janeway and Jackson with like results In other experiments, they retarded the arterial circulation by placing an adjustable clamp on the abdominal aorta After maintaining a low arterial pressure of about 50 mm Hg for two or three hours, the clamp was removed Shock developed in these dogs after the reestablishment of the circulation This procedure did not involve in any way the blood supply to the brain, cord, heart or vasomotor apparatus, hence the results cannot be explained as originating in either of those structures These authors were among the very few who recorded postmortem observations after their experiments They noted marked engorgement of the veins and capillaries, stasis, petechial hemorrhages, transudation of plasma and other visceral changes exactly like those which my associates and I later described as the pathologic changes characteristic of shock

They noted also that the venous pressure and plasma volume declined There was a loss of total blood volume, ranging from 30 to 50 per cent, accompanied by increased concentration of the blood They explained this as the result of stasis of blood in the

capillaries in the viscera, with increased permeability of the capillaries allowing transudation of the plasma into the tissue spaces. These features were noted visibly during the development of shock before a decline in the blood pressure occurred These authors came remarkably near to an accurate solution of the mystery of shock Their investigations lacked only a comprehension of the capillary reactions entailed and of the significance of the accompanying pathologic features No criticism is implied by this statement, for the major principles of capillary physiology have been established subsequent to their reports. Being physiologists they were hesitant, perhaps unduly, to advance interpretations of the abnormal morphologic features which they described so accurately

Mann produced circulatory obstruction by a different technique He placed a ligature about the veins and lymph vessels leading from the dog's limbs, but did not ligate the arteries This produced complete passive congestion and stasis of blood in the areas involved After varying periods of time the ligatures were removed and the circulation reëstablished Varying degrees of shock developed and death resulted if the stasis was allowed to continue long "The results following the release of the ligature are due to damage to the tissues in the involved areas and the passage of toxic products from the injured tissues into the general circulation Obviously the damage resulted from anoxia since no mechanical trauma was done

Cannon and Cattell arranged a mechanical device by which varying degrees of hydrostatic pressure could be exerted on the outside of the heart This enabled them to limit the cardiac output by limiting its diastolic intake and thereby to bring the arterial pressure down to any desired level This impediment to the circulation decreased the delivery of oxygen to the entire system When pressures below 80 mm Hg had been maintained for some time the pressure continued to decline without further artifice

Allen obstructed the circulation to the limbs of animals by placing a rubber tourniquet tightly about the limb No systemic disturbances developed so long as the tourniquet was in place After several hours obstruction, the removal of the tourniquet was followed by shock which progressed regularly to a fatal termination These experiments were essentially like those of Mann except that in these no surgical procedures and no anesthesia were used

The evidence cited indicates that mechanical retardation of the circulation, if sufficient to interfere seriously with the delivery of oxygen, will cause shock. When anoxia affects the entire system, or a large part of it, the direct effect of it upon the capillaries creates a circulatory disturbance. The sequestration of blood in the engorged capillary stream bed reduces the return flow of venous blood to the heart, causing a low volume output. Permeability of the capillaries allows leakages of plasma into the tissue spaces, reducing the blood volume and causing hemoconcentration. In some of the experiments described, it appeared that products of abnormal cellular metabolism, due to anoxia, affected the systemic circulation when admitted to it.

Epinephrin Shock.—A number of workers have found that the maximum or prolonged effects of epinephrin will produce shock indistinguishable from that resulting from other causes. Bainbridge and Trevan found that the slow injection of epinephrin into anesthetized dogs produced a state of shock. Hemoglobin and hematocrit readings showed concentration of the blood and loss of plasma volume. In one instance the hemoglobin percentage rose from 95 to 129, accompanied by an increase in the viscosity of the blood from 6.8 to 9.1. There was an increased flow of lymph from the thoracic duct and the arterial blood pressure declined. They found no difference between these effects of epinephrin and those of histamine upon the circulation.

Erlanger and associates produced shock in dogs by repeated injections of epinephrin in large doses. The results corroborated those of Bainbridge and Trevan. There were progressive loss of plasma volume and corresponding concentration of the blood, followed by circulatory deficiency and death. Postmortem examinations showed marked capillary and venous congestion in the viscera, stasis and edema, and numerous petechial hemorrhages in mucous and serous surfaces. They found no points of difference between shock produced by epinephrin and that produced by other means. Lamson found a marked increase in the number of erythrocytes in the blood of animals following injections of epinephrin. He attributed this to capillary permeability with leakage of plasma into the tissues.

It seems probable that the mechanism of epinephrin shock is the same as that from mechanical retardation of the circulation as described in the preceding section. Epinephrin in large doses may produce arterial constriction of such degree and duration that the tissues suffer lack of oxygen. Such anoxia would lead to capil-

lary atony, transudation of plasma, loss of blood volume stasis and hemoconcentration as readily as would anoxia otherwise produced.

HYPERACTIVITY OF THE SYMPATHO-ADRENAL SYSTEM

The fact that large doses of epinephrin will cause the complete syndrome of shock is the foundation for the theory that this may be a prime factor in shock from sundry causes Various stimuli such as pain, fright or other strong emotions, burns, trauma anesthesia and the effects of certain drugs, evoke activity of the sympatho-adrenal system This is evidenced by increased cardiac action, arterial vasoconstriction and high arterial pressure, increased blood sugar pallor dilated pupils, perspiration and by other signs. It is recognized that each of these features are present in the early stages of shock before evidences of circulatory deficiency appear The compensation of any threatened disparity between the volume of blood and the volume capacity of the vascular system is accomplished largely by the physiologic responses mentioned

In view of these considerations, it is held that *hyperactivity*, accompanied by prolonged maximal arterial constriction, may cause shock by the same mechanism as large doses of epinephrin This has been suggested as the explanation for shock resulting from wounds accidental injuries abdominal emergencies, surgical procedures and burns. Hemorrhage and local transudation of fluid from the blood into the area of injury are recognized as important contributory factors

Freeman and his associates were early proponents of this theory It has been supported by Harkins, Davis, Tomb Scudder and others and has been accepted by many as the long sought solution of the problem The theory is attractive and is in harmony with several well established principles If no invalidating evidence should appear the processes described would provide a satisfactory explanation for shock However a critical examination of the evidence reveals several points of seeming incompatibility with known facts

It has not been shown that the quantity of epinephrin necessary to produce shock could be derived from the animal's own adrenal glands within the time limits of the experiment.

When men or animals are in mortal combat it is probable that

their sympatho-adrenal systems are called into maximal activity Yet no instances are reported in which shock developed after prolonged combat, in the absence of hemorrhage or of serious physical injury

One effect of adrenalin is to *increase* the coagulability of the blood while on the other hand, this is *markedly reduced* during shock Blood from patients or animals in that condition often will remain unclotted for hours

If arterial vasoconstriction were an important primary factor initiating shock, one would expect that syndrome to develop occasionally in cases of so-called essential hypertension The latter condition is attributed to excessive arterial vaso-spasm, resection of sympathetic nerves and ganglia is sometimes performed for its relief Circulatory disturbances of the shock type are not recorded as sequelæ of hypertension

Severe pain or stimulation of sensory nerves calls the sympatho-adrenal system into immediate activity But conditions accompanied by prolonged intolerable pain, such as renal or biliary colic, do not cause shock nor can it be produced experimentally by prolonged excessive mechanical or electrical stimulation to sensory nerve trunks (Porter, Janeway and Ewing, Mann, Seelig and Lyon, Wiggers, Phemister and others) The cutting of the cord or severing of nerve paths to the brain does not prevent the development of shock from trauma or from manipulation of the intestines

A bullet wound of the abdomen with penetration of the bowel will result in shock with great regularity, while similar wounds without penetration may not do so The sympatho-adrenal response should be of similar degree in both types of wounds

An extensive superficial burn will result in shock in a degree proportional to the severity and the area of the burn If treated promptly, as with tannic acid, shock may not develop or will be of lesser degree It is not probable that local treatment with tannic acid reduces the activity of the sympatho-adrenal system

Adrenalectomized dogs, maintained in a normal physiologic state by injections of cortical hormone, can be thrown into shock readily by the various agents which cause shock in normal dogs (Swingle and associates) Such animals are *hypersusceptible* to anaphylaxis, trauma, burns, hemorrhage and to various capillary poisons Obviously, adrenal hyperfunction is eliminated as a factor by the conditions of these experiments

Dogs which have been subjected to bilateral sympathectomy develop shock from trauma, or from manipulation of the intestines, as readily as normal dogs (Freedlander and Lenhart)

It has not been shown that the sympatho-adrenal system is called into hyperactivity by intravenous injections of peptone histamine, venoms, bile salts, sundry poisons or by anaphylaxis Yet shock develops under such conditions with almost explosive suddenness and with maximum severity Circulatory failure develops more gradually after injections of epinephrin

Finally, it has been shown (see Chapter XII) that deep roentgen irradiation of the abdomen causes the complete and characteristic syndrome of shock This is accompanied by hemoconcentration and the postmortem visceral changes are those distinctive of shock. Roentgen irradiation causes delayed necrosis of the glandular epithelium in the intestinal mucosa. Extensive disintegration of the cells occurs after two or three days, the onset of symptoms is correspondingly delayed It appears that absorption of products from the tissues damaged by x rays results in progressive deficiency of the circulation These experiments have a significant bearing upon the mechanism of shock. Whatever fright or other emotional response occurred incident to the treatment, had subsided The treatment was painless and the dogs appeared entirely normal on the following day No anesthesia was used, nor was there hemorrhage nor local loss of fluid Such conditions provide no apparent cause for the development of sympatho-adrenal hyperactivity several days subsequent to the irradiation

Recently Wiggers reviewed critically the various theories proposed as explanations for shock Concerning vasoconstriction as an important causative factor, he stated "there is no substantial evidence that it (vasoconstriction) is sufficiently generalized or intense enough to cause the capillary damage which this hypothesis requires

The chief experimental evidence supporting this theory was derived from a comparison of the effects of hemorrhages and transfusions in two groups of dogs (Freeman and associates) For reasons not entirely clear, the normal dogs were subjected to far greater losses of blood than the sympathectomized ones Yet the authors concluded that the latter were more resistant to the effects of hemorrhage Since shock and the effects of hemorrhage are not identical (see Chapter IX), these experiments do not bear directly upon the problem Recently Freeman and his co-workers

produced shock by trauma in totally sympathectomized dogs and stated that those results could well be explained on the basis of toxic substances absorbed from the area of trauma.

It is probable that hyperactivity of the sympatho-adrenal system may be a factor of importance in a few limited types of conditions such as acute pancreatitis or the perforation of abdominal viscera. The escape of highly irritating digestive juices may cause a maximal prolonged response by the sympatho-adrenal system, and may account for the primary shock merging into secondary shock without interval. However, it appears that more convincing evidence will be required before this theory can be accepted as an explanation of shock in general.

The Vicious Circle.—It has been noted that if the blood pressure remains below a certain level for a relatively short time the circulatory deficiency tends to progress. This is called the *critical level* because with lower pressures the condition acquires a self-perpetuating quality having the features of a vicious circle.

Starling's investigations on the physiology of the circulation indicated that when the arterial pressure is below 80 mm. Hg the heart itself receives an insufficient supply of arterial blood. Anoxia of the myocardium diminishes its output of energy and lowers its functional efficiency.

Hill and McQueen noted that when the blood pressure is reduced to about 80 mm. Hg there is a tendency for stasis to develop in capillary areas, and the minute vessels become choked with closely packed corpuscles. Anoxia develops, the osmotic pressure in the tissue rises and the tissues imbibe fluid from the blood within the capillaries. Less blood is returned to the heart and the circulatory deficiency increases.

Cannon noted evidence of the operation of a vicious circle in the condition of wounded soldiers and attributed this to a combination of factors. When the pressure is reduced below a critical level, *i. e.*, between 70 and 80 mm. Hg, the oxidation and the metabolism are lowered and the production of heat is diminished. Low temperature contributes to increased viscosity of the blood. Transudation of plasma has the same effect by increasing the concentration of the blood, and the increased friction of thick, viscid blood further impedes circulation. As more blood stagnates in capillary areas, the volume of return flow is diminished and the volume flow of arterial blood is reduced. This lowers the *vis a tergo* by which blood might be forced through the capillaries. As the circulation

lags, the supply of oxygen to all tissues including the myocardium is further reduced and the condition is thereby self perpetuating

Anoxia is a most important factor in the vicious circle because it plays a dual rôle as both cause and effect ✓ *Anoxia will cause circulatory deficiency and circulatory deficiency will cause anoxia* ✓ In this relationship the condition of dilatation and permeability of the capillaries plays a reciprocal rôle of equal importance

When lack of oxygen in an area of tissue renders the capillaries atonic and permeable, plasma escapes into the tissue and stasis develops in the vessels. This further impedes the circulation, decreases the volume flow, lowers the blood volume and increases the anoxia. It is evident that either of these factors, operating alone, brings the other into action *This reciprocal relationship* constitutes a self perpetuating mechanism which operates as a vicious circle It is illustrated visually in the accompanying diagram (Fig 3)

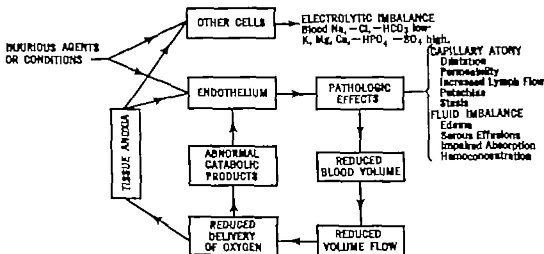


FIG. 3 —Various noxious agents, acting upon endothelium, produce capillary atony and derange the mechanism of fluid balance. A consequent reduction of blood volume and of volume flow reduces the delivery of oxygen, resulting in tissue anoxia Lack of oxygen affects endothelium injuriously both directly and by producing abnormal metabolites. These effects cause dilatation and permeability thereby introducing the self perpetuating quality of a vicious circle.

The effects of injurious agents or of anoxia upon OTHER CELLS causes changes in electrolytic permeability as illustrated in Figure 2, p 36. These effects cause electrolytic imbalance and changes in the chemistry of the blood which are characteristic of shock.

Summary ✓—The dynamics of shock include the operation of several deleterious factors Most important among these are

endothelial damage and *anoxia* because the development of either of these will presently bring the other into action This reciprocating effect gives the disorder a self-perpetuating quality, it operates like a vicious circle, tends to progress and may lead to irreversible changes

Prolonged vasoconstriction, as by epinephrin, may cause a degree of anoxia sufficient to initiate the action described This will produce the syndrome of shock, complete in all essential particulars

This effect of epinephrin is believed by some to be an important initiating factor However, there are many reasons why hyperactivity of the sympatho-adrenal system does not explain adequately the mechanism by which shock usually occurs

CHAPTER V

THEORIES CONCERNING SHOCK

THE mechanism by which the circulation, fluid balance chemical concentrations and other physiologic conditions are disordered has been discussed and the reciprocal effects of *capillary atony* and *anoxia* have been set forth It will now be of interest to trace the development of knowledge concerning the etiology of shock Until quite recently, a pronounced decline in arterial pressure was regarded as the central and most important feature in the syndrome. Every possible cause for the low blood pressure —cardiac inefficiency vasomotor weakness, deficiency of the "veno-pressor mechanism," adrenal insufficiency, hemorrhage and loss of fluid from the blood—each has been advocated as the primary cause for the condition None of these explanations, some of which were most plausible and were supported by experimental evidence as well as by logic, received confirmation when tested by carefully controlled experimentation In each instance factual evidence subsequently was developed invalidating the theory under consideration

Several items from the associated physiologic disturbances have been proposed as prime causative agents some have incriminated the decreased alkaline reserve, others the low chloride content of the blood, and still others its high content of potassium Recently, arterial vasoconstriction has been advocated as initiating the vicious circle That other items seen in the syndrome of shock may yet be proposed as causes, is not improbable In this, as in attempts to solve other difficult problems, it is not strange that effects should sometimes be mistaken for causes

The net result of the researches and studies made in supporting and testing these various theories, has been a great amount of valuable factual information These facts must be integrated in proper relationship to each other, like the pieces of a jig saw puzzle each must fit into an appropriate place and must serve to complete the picture Incompatibility with any known fact will invalidate any hypothesis

Historical.—Le Dran (1743) applied the term *shock* in a mechanical sense to the effects of a bullet striking with 'such rapid Force that the whole Animal Machine participates in the Shock

and Agitation " The word was used in that sense by several early writers Latta (1795) used the term in describing the effects of electric current upon a patient, and the same term later was applied indiscriminately to mechanical impacts, fright or grief as the effects of a horrible sight or of sad news, the effects of electricity, and to the profound depression or "wound torpor" which developed after severe burns or trauma Shock has been used to describe almost any condition associated with sudden or rapidly developing weakness or syncope

The early attempts to account for shock were like all human efforts to explain disease and other natural phenomena by supposition and by processes of logic The early writings abound in such hypothetical concepts as "draining of vital fluid," "destruction of the great nervous power," "disorganization of vital functions," "commotio cerebri" and the like An analysis of the theories current before the advent of experimental medicine, would be time-consuming and profitless The great surgeon and pathologist, Samuel D Gross, described accurately the clinical manifestations of shock His explanation of its origin may be cited as representative of the theorization of that period (1872) He wrote

> Shock is a depression of the vital powers, induced suddenly by external injury, and essentially dependent on loss of innervation It bears the same relation to the nervous system as syncope to the vascular In the one case the result is caused by a diminution of the nervous fluid, in the other by a diminution of the blood In both the consequence is more or less prostration The blood has long been known by physiologists as the vital fluid so necessary to the well being of the system But it is certainly not the only fluid entitled to this distinction, the nervous fluid is both more subtle and more important as a life preserver When blood flows away in a mighty and overwhelming torrent life is destroyed by the excessive sanguineous drainage But in shock the same effect may happen, and yet the body be literally surcharged with blood, not a single drop, perhaps, having been spilled in the accident causing the fatal result Thus of the two fluids the nervous is the more important, because the more essential to life, and its disturbance is therefore a more frequent cause of death

He criticized severely the practice of bleeding in shock, as contrary both to physiology and to common sense, and added the observation that when such is attempted by the ignorant the blood generally refused to flow, and consequently no harm was done Evidently the decreased volume flow of blood in peripheral parts had impressed Gross

Various hypotheses advanced during this period, were combinations of functional disturbances of the nervous system with reflex inhibition of the action of the heart, respiration and of vascular tonus At that time it was not realized that neither the heart nor the respiration is paralyzed or inhibited in shock Those interested in these theoretic dissertations will find them summarized critically in a monograph by Groeningen (1885) Some of his conclusions are not harmonious with subsequent developments, but his analysis of the evidence then available makes this the outstanding contribution of that period

The clinical features of shock were clearly stated and the similarity of these signs to those of hemorrhage was recognized. Failure to differentiate between shock and sudden death from other causes was cited as a source of confusion and of statistical inaccuracies Fat embolism, coagulation and other changes in the blood were rejected as causes. Poor instruments and unskillful manipulation, fatigue and deprivation, lowered resistance from hemorrhage, disease, alcoholism or undernourishment, anxiety, restlessness and fear on the part of the patient, improper bandaging, uncareful handling and rough transportation of the wounded were stressed as contributing factors. The presence of these factors justified delay in operation, and the use of stimulants and rest in a warm bed were advised in the interim He stated that an interval of a few hours usually occurred between the injury or operation and the development of shock, but if the latter did not develop within twenty four hours it seldom occurred later These observations received remarkable confirmation during World War I thirty years later

VASOMOTOR EXHAUSTION

Groeningen found that previous hypotheses were contrary to physiologic evidence and sought for a satisfactory explanation in dysfunction of the vasomotor mechanism He reasoned that any traumatic insult produces exhaustion of nerve centers and decreased reactions. The summation of the stimulations arising from preceding disease, from the injury or operation itself and from subsequent events, causes exhaustion of the vital centers particularly in the medulla This results in vasomotor deficiency accompanied by vascular relaxation All the manifestations formerly attributed to reflex inhibitions and reflex paralyses, were thus explained to his satisfaction

Crile's researches on shock were based upon the theory of vasomotor exhaustion, although he neglected to credit Groeningen with originating that hypothesis He produced shock in dogs by various combinations of trauma, irritation of nerves, manipulation of viscera and other forms of tissue abuse His records showed that the immediate effect of various forms of injury was an *increase* in blood pressure which indicated vasomotor responsiveness and activity But after prolonged repeated injuries the pressure declined and the circulation became ineffective This suggested a loss of vasomotor activity which was attributed to exhaustion

He believed that repeated painful stimulation eventually caused exhaustion of the vasomotor centers in the cord and medulla, as a result of which the reflexes became weakened until finally arterial relaxation occurred He held that these effects were produced even under complete anesthesia when no consciousness of pain was present A corresponding fall in venous pressure was demonstrated and the circulatory defect was attributed to an insufficient return of venous blood to the heart

Subsequent investigations failed to support vasomotor exhaustion as an adequate explanation Forbes and Miller showed that surgical anesthesia interrupts the passage of stimuli from the periphery to the brain, consequently no exhaustive effects would be produced Cannon cited the fact that shock follows wounds in which little or no pain was felt, and fails to develop in conditions such as neuritis, biliary or renal colic, in which pain is intense and prolonged He found no evidence indicating that either pain or vasomotor failure is a factor in the development of shock Freedlander and Lenhart traumatized the thighs of dogs whose cords had been severed, and whose abdominal sympathetic ganglia had been excised Shock was produced in these as readily as in normal animals

Many workers (Porter, Janeway, Ewing, Mann, Selig, Joseph, Lyon, Wiggers, Phemister and others) found that prolonged stimulation of afferent nerves uniformly failed to produce a condition resembling shock Several of these writers observed that, during experimental shock, the arteries are not dilated but are maximally contracted The same was noted in human cases of shock (Malcolm, Fraser, Cope and others)

Erlanger and associates found no evidence of loss of vasomotor tone in shock produced by any method In the early stages, the vasomotor tone was definitely increased and there was evidence of vasomotor activity even at the end of long experiments The

loss of vasomotor tonus, which finally occurred as the animals died, was explained as a result of, not as a cause for, the prolonged low blood pressure

In the terminal stage of shock when the blood pressure has been below the critical level for some time, the entire organism suffers from lack of oxygen This deficiency affects the nervous system as well as other parts Reflexes are abolished, there is no response to painful stimuli, the subject is lethargic or semi comatose, the respirations become weak and shallow and the blood pressure declines to zero Apparently this terminal stage is the only period when vasomotor deficiency is present in shock

ACAPNIA

Henderson's studies on the physiology of shock showed that the earliest evidence of it is a decrease of from 40 to 70 per cent in the amplitude of the cardiac output This decrease, described as reduced volume flow, occurred regularly before any decline in blood pressure took place It was not due to cardiac inefficiency but to a decreased return flow of venous blood to the heart. The deficiency, as he saw it, originated in the "veno-pressure mechanism' which controls the return flow of venous blood. He believed that this is activated by the CO_2 of the blood, that if the latter falls below normal the venopressor mechanism becomes inactive and a deficiency develops in the return flow of venous blood from the periphery He reasoned that increased respiratory activity caused by painful stimuli, leads to a depletion of CO_2 in the blood—acapnia—which produces inactivity of the venopressor mechanism This results in decreased cardiac output low blood pressure failing circulation, asphyxia of the tissues and produces the syndrome of shock

This plausible interpretation was widely accepted but, when subjected to the test of controlled experimentation, it received little confirmation Mann attempted unsuccessfully to produce shock from hyperventilation of the lungs by Henderson s technique In other experiments shock was induced by inserting the hand through an incision into the abdomen the skin was then tightly clamped about the wrist and a constant stream of CO_2 was passed directly into the abdomen while the intestines were manipulated This precaution did not prevent nor retard the development of shock

Janeway and Ewing provided a rebreathing apparatus whereby the CO_2 content of the blood was maintained within normal limits In other cases they kept the CO_2 content of the blood above normal by supplying CO_2 from a tank through a respirator Shock was induced in these animals as readily as in those in which no such precautions were used From various experiments they found no evidence that a diminution in CO_2 is a causative factor in shock Wiggers likewise was unable to confirm the hypothesis of acapnia Coonse and his collaborators found that when an animal in shock was given inhalation of CO_2 his condition became rapidly worse

Cannon pointed out that the assumption that wounds cause marked increase in respiratory activity is invalid The severely wounded regularly state that they suffered no pain at the moment of being struck When questioned, they usually testify to having felt a dull blow, but not severe pain Crushing and tearing agents seem to deaden the nerves for some distance back of the exposed surface Pain begins to appear in such instances only with the development of inflammation

In the severely wounded also there is absence of such vigorous breathing as Henderson's theory requires Cowell paid particular attention to the respiration of severely wounded men and never observed hyperpnea In the casualty clearing stations the typical form of breathing, though faster than normal, was superficial Furthermore, even when the most extreme hyperpnea is carried on voluntarily, no shock-like condition results In cases of almost intolerably severe pain, such as is experienced in facial neuralgia, no shock-like phenomena are produced

The foregoing observations invalidate the view that shock is associated with intense pain and with such respiratory activity as to pump out the CO_2 from the blood Pain and the excessive breathing required for acapnia are commonly absent, shock may exist without acapnia and acapnia may exist without shock The low CO_2 content of the blood in shock may be accounted for as the result of the low blood pressure, not as its cause

Finally it should be mentioned that shock resulting from injections of histamine, of peptone, of tissue extracts, of bile, from the introduction of muscle substance or of extracts of muscle into the peritoneal cavity, or from anaphylaxis, cannot be explained satisfactorily on the basis of lowered CO_2 content of the blood or of the tissues

DECREASED ALKALI RESERVE

Henderson (1910) had observed that deficient oxidation was a prominent feature in experimental shock and suggested that this would reduce the alkalinity of the tissues and of the blood Crile (1915) included shock among the clinical conditions in which acidosis is an important factor Cannon (1918) found a marked decrease in the alkali reserve in cases of traumatic shock, of severe hemorrhage, and of gas bacillus infection But no reduction of the alkali reserve was observed until the blood pressure had declined to 90 or 80 mm Hg Also in experimental shock produced by limiting the cardiac output, the alkali reserve declined only after the blood pressure was reduced below 80 mm Hg "Air hunger" was manifested when the acidosis was extreme

The question at issue is not the fact of such a decrease, but its interpretation Is this decrease a causative factor or is it merely a result of the physiologic disturbances which constitute the syndrome called shock?

McEllroy found a gradual decrease in the reserve alkalinity in experimental shock In no case did the decrease precede the development of shock nor was the change in the reserve alkalinity sufficient to account for the condition of the animal In experimental acidosis produced by intravenous injection of lactic acid the alkali reserve was lowered to the degree found in shock without producing any marked symptoms in the animal When by further injections the animals had been reduced to a terminal state treatment by injections of sodium bicarbonate solution resulted in prompt recovery Similar injections in animals in shock produced no benefit. The maintenance of the alkali reserve at normal levels by injections of sodium bicarbonate solution did not prevent the development of shock He concluded that acidosis is not a cause but is a secondary associated condition Guthrie arrived at the same conclusion from experiments of similar kind

The Special Committee for the Study of Shock and Allied Conditions investigated the relationship between acidosis and circulatory deficiencies. Lactic acid was given slowly by intravenous injection until the CO_2 combining power of the plasma declined from 46 4 to 10 3 volume per cent Discontinuance of the injection was followed promptly by a rise in the CO_2 carrying capacity and although the amount of acid received was much above that which could result from metabolic processes, the animal did not develop shock In other experiments injections of lactic

lipemia and fat embolism Among the conditions of its occurrence were listed comminuted fractures and other injuries to bone extensive surgical procedures severe physical trauma, acute peritonitis and burns of the skin The symptomatology of fat embolism resembles that of shock. It includes restlessness, falling or rising temperature, dyspnea, signs of pulmonary edema, blood tinged frothy sputum and collapse The pathologic features which he described are indistinguishable from those found regularly in shock from causes which excluded fat embolism Some of these are congestion of the lungs and other viscera, edema, and miliary hemorrhages in the heart, brain kidneys and elsewhere One has the feeling that many deaths attributed to fat embolism were in fact due to circulatory failure of the shock type

Porter injected olive oil or thick cream intravenously in cats This was followed by a decline in blood pressure and other manifestations which he interpreted as analogous to traumatic shock in man Bissel injected dogs intravenously with varying amounts of olive oil The first injections were without effect Larger and repeated injections caused finally a sudden *rise in venous pressure* and a gradual fall in arterial pressure followed by death These results were confirmed by Simonds, but the amount of olive oil necessary to produce this effect was about 2 cc per kilogram of body weight Later Porter produced a fall in blood pressure by injecting fats into the vertebral arteries, and argued that the circulatory phenomenon of fat embolism resulted from the plugging of capillaries in the medulla by particles of fat

Wiggers studied the effects of injections of fats into the circulation both arterial and venous and found them extremely variable but in neither case did they produce the circulatory phenomena of traumatic shock Crile regarded the theory of fat embolism as an inadequate explanation He noted that shock followed abdominal injuries which penetrated the viscera but did not follow similar injuries in which no penetration occurred, though the same areas of fatty tissue had suffered similar trauma He called attention to the occurrence of shock after burns and after injuries to the head and chest, in which conditions no fatty tissue had suffered trauma

Other discrepancies further invalidate the theory The plugging of pulmonary capillaries causes distention of the systemic veins and increased venous pressure In shock there is decreased venous pressure and the systemic veins are collapsed and relatively blood less The production of shock by manipulation of the intestines,

by injection of peptone, of fat-free tissue extracts, of histamine or by anaphylaxis, indicates that the entrance of fat into the blood stream is not an essential factor in the production of shock This conclusion does not contradict the fact that under some conditions fat may enter the blood stream in quantities sufficient to affect the circulation seriously, or even to cause death Such occurrences are rare, and should be differentiated from traumatic shock In reviewing the published clinical reports of fat embolism, one is impressed by the probability that many of the cases described were in fact traumatic shock and were attributed to fat embolism on insufficient evidence

The evidence cited supports the conclusion that fat embolism is not an adequate explanation for the mechanism of shock

Such was the status of the problem prior to the investigations made during and immediately following World War I Progress up to this time consisted in establishing many pertinent facts and in eliminating several proposed explanations as inadequate

CHAPTER VI

TRAUMATIC TOXEMIA

The danger of shock constantly haunts the surgeon This grave complication may follow extensive operative procedures, burns and traumatic injuries of various kinds It becomes a major problem for those who have to deal with accidental injuries, and for military surgeons in the management of battle casualties It occurred on a huge scale during World War I and the British Medical Research Committee organized an international coöperative effort to elucidate its mechanism Eminent surgeons, physiologists, pharmacologists and internists of England, France and the United States, made a combined attack upon various salients of the problem The plague of war provided opportunity for clinical studies such as a great epidemic disease would furnish for investigations on its cause and nature. Observations on shock in wounded men were compared and checked with the results of experimental studies employing the methods of physiology and pharmacology

Unfortunately pathologists were not concerned with this coöperative endeavor and the results of clinical observations and of laboratory experiments were not reinforced by morphologic studies The belief had been accepted without question that shock is purely a physiologic disturbance, unaccompanied by characteristic morphologic changes.

The reports of the various investigations were correlated and summarized by Cannon in his monograph *Traumatic Shock* The experiences of the military surgeons, and of others who made studies on wounded soldiers, are of the highest importance Battle casualties provided an almost unlimited supply of clinical material and this was utilized for investigations both on the nature and on the practical management of shock

OBSERVATIONS ON WOUND SHOCK

Shock developed in its simplest and least complicated form after extensive damage to the muscles and bones of the peripheral parts, uncomplicated by serious hemorrhage Extensive deep injuries from large shell fragments and multiple injuries from small fragments and from bullets, without penetration of viscera,

provided this type of material. The conservative treatment of such wounds was followed by a high mortality from shock and from subsequent infections. This experience led the surgeons to adopt more radical measures. Badly damaged limbs were amputated and *débridement* was practiced on other severe wounds. This consisted in excising all bruised or lacerated tissues, all projecting tags and all tissues infiltrated with blood—in other words, removing all débris. This left a larger area to be healed but it was lined on all sides by clean, healthy, viable tissue.

These measures caused immediate improvement in the condition of the wounded, and both the incidence and the severity of shock were materially reduced. Wallace stated: "This procedure is often the initial step in an extraordinary improvement in the patient's state. . . . Experience proves that the exclusion of the focus of injury by short and radical procedures causes the symptoms of shock to disappear." McNee stated: "The operation is commonly followed by a remarkable and maintained improvement, so rapid and striking as to appear a direct sequel to the removal of the damaged limb." These experiences are corroborated in the surgical and medical histories of the American and of the British armies during the war.

Quénu published an extensive analysis of the experiences of the French military surgeons. They observed that everything favoring absorption from the injured area favored the development of shock. It developed most readily when the area of damage communicated with the surface by only a small opening. The time elapsing after injury before surgical treatment of the wounds was an important factor. Sante reported a large series of similar severe wounds in which the mortality was only 11 per cent when operated upon within three hours. The mortality rose progressively to 75 per cent following delays of eight to ten hours. It was the experience of the French surgeons that early amputation or débridement of the wounds minimized the absorption of toxic substances from the areas of injured flesh, and that delay increased such absorption to dangerous degrees.

Results from the use of tourniquets were like those from experimental obstruction of the circulation (Mann, Allen, Chapter IV). Frequently tourniquets were applied by the litter bearers as they collected the wounded, and were still in place when the latter arrived at the field hospitals. If in such cases the tourniquets were removed, shock often developed immediately. Results of this kind occurred so frequently that orders were issued against the

use of tourniquets to control hemorrhage Their use to prevent the development of shock was sanctioned 'The suggestion is offered that if a limb has been so badly mangled that it cannot be saved a tourniquet should be set close above the trauma and left in place until after amputation The amputation should be performed proximal to the tourniquet. Thus the body is protected against toxic material which is present in the torn and smashed tissues and is likely to be absorbed '

Contributory Factors —It was noted by the military surgeons that many factors incidental to the circumstances of warfare contributed to the development of shock These included the mental strain and stress of battle loss of blood from wounds pain fatigue hunger and exposure to cold Often the wounded had lain for hours before removal to first aid stations Imperfect immobilization of fractured limbs rough journeys on litters or in ambulances and long delays before surgical attention could be given, were found to increase seriously the gravity of the after effects of wounds

Frequently the administration of an anesthetic precipitated circulatory failure in those who showed no signs of shock and whose apparent condition was not serious Better results were obtained by postponing operation temporarily until following rest warmth hot food and stimulants the patient was better able to withstand anesthesia and operative procedures The appropriate operation was then done as rapidly as possible thereby reducing to a minimum both the anesthesia and the operative procedures Frequently a transfusion of blood or an intravenous infusion of fluids was given prior to the operation Such precautions were found effective in reducing both the incidence and the severity of shock

As experiences in the treatment of wounded soldiers accumulated the conviction grew that the absorption of products from injured tissues was a major factor in producing the circulatory deficiency which followed Often this deficiency was out of all proportion to the apparent severity of the wound and subsided in a remarkable fashion after the amputation of a mangled limb or the débridement of other wounds

Studies were made on other than the surgical aspects of shock Examination of the blood of wounded soldiers showed progressive hemoconcentration as shock developed and hemodilution after hemorrhage The surgical and medical staffs applied this test to the differentiation of those conditions and used it practically in

estimating the severity of shock and the degree of the operative risk

Keith showed that, after severe wounds, the recuperative capacity depended on the ability of the circulation to take up and to retain fluid In one class of cases the circulation was able to absorb fluid from the tissues and to retain fluid supplied therapeutically There was no circulatory decompensation in these cases and they responded readily to treatment In another class, the capacity to absorb fluid was lost but the vascular structures could still retain fluid if supplied in suitable form In profound shock there was failure of compensation for the circulatory deficiency, the normal process of blood dilution failed to operate and the vascular structures were incapable of retaining colloid solutions or even whole blood Treatment was entirely ineffective in this class of cases These observations are highly significant as indicating both a serious derangement of fluid balance and failure of the mechanism of absorption when shock is fully developed

EXPERIMENTAL EVIDENCE

The interpretation that substances absorbed from injured tissue in some way cause circulatory failure, originated from observations on inestimable numbers of battle casualties Investigations of another type were designed to test that interpretation and to determine, if possible, the mechanisms involved

Bayliss and Cannon produced shock in cats by mechanical trauma to the muscles of the thighs This was followed by a fall in blood pressure, increase in the pulse and respiratory rates, a diminution in the CO_2 combining power of the plasma, a decrease in the total blood volume and an increase in the erythrocyte count of the blood In such animals, massage of the damaged muscle caused a further decline in blood pressure The previous severance of the lumbar cord did not prevent shock following trauma to the thigh muscles Evidently the fall in blood pressure was not due to painful stimulation acting upon the central nervous system nor to any mechanism dependent upon nerve communications to the injured area Shock did not occur if all the vessels of the legs were ligated but occurred promptly following the release of such ligatures Examinations of the lungs for fat failed to show any evidence of fat emboli

Bayliss made an extract of tissue by boiling muscle substance

in saline solution When this was given intravenously it produced a prompt fall in blood pressure accompanied by visible dilatation of the minute vessels of the intestines There was a progressive increase in the concentration of the blood as shock developed in these animals, as in wounded men

Dale, Laidlaw and Richards were led to make experiments with histamine because of the fact that it produces a shock like failure of circulation when injected into the blood stream Cats under ether anesthesia developed shock promptly following the injection of a milligram or two of histamine The red cell count, hematocrit determinations and hemoglobin percentage indicated a marked concentration of the blood as shown by a loss of 50 to 60 per cent of the original plasma volume The authors concluded that the decreased volume of blood resulted partly from transudation of plasma through capillary walls which had been rendered abnormally permeable by the action of histamine and in part by stasis of blood in the dilated capillaries Direct inspection of the internal organs supported this view The arterioles down to the finest branches were contracted but the viscera showed diffuse dusky congestion and the smallest venules were distended with dark blood. They interpreted the effects of histamine as due to the sequestration of blood in the dilated capillaries and venules of the viscera. They believed that loss of the normal tone of the capillary walls is the essential cause of this condition They recognized that histamine typifies the action of products of protein cleavage resulting from various causes "The action of histamine does not stand by itself but represents in most characteristic features a type of action common to a large group of substances of animal or bacterial origin They attributed the effects of all these chemically unrelated substances to loss of tone and increased permeability of capillary endothelium The conclusions of the Committee on Wound Shock are summarized by Cannon

> The theory of secondary shock which has the strongest support, both in clinical observations and in laboratory experiments, is that of a toxic factor arising from damaged and dying tissue and operating to cause an increased permeability of the capillary walls and a consequent reduction of blood volume by escape of plasma into the lymph spaces. Thus the concentration of the corpuscles is also readily explained It is recognized that after a sufficient time infection may occur and be of such character in itself as to induce a persistent low blood pressure. According to this theory there might be no essential difference between the effects of toxins given off by damaged tissue and of toxins resulting from activity of bacteria.

COLLATERAL EVIDENCE

Most of the increased knowledge concerning capillary physiology referred to in Chapter I, has developed since the previous World War The fact that students of capillary reactions were not interested primarily in shock, and that their investigations were not designed to test any theory as to its origin, does not lessen the significance of the evidence from these sources

Ebbecke's studies on dermographia[1] showed that local urticarial reactions are characterized by dilatation and engorgement of capillaries, and by edema resulting from permeability of the capillary walls He showed that various forms of injury to tissue cells cause them to release cytoplasmic substance to which the capillary endothelium is physiologically sensitive In response to the cytoplasmic substance, which may be liberated either by irritation, injury or functional activity, the adjacent capillaries relax and their walls become permeable to colloids, allowing the escape of plasma into the tissue spaces

Certain colloidal dyes are used by physiologists for demonstrating local permeability of capillary walls These dyes escape into the tissue spaces if the endothelium is abnormally permeable but they are retained in the blood for many hours and cause no local staining of tissues under normal conditions If a colloidal dye, as trypan blue, is injected into the blood during the formation of a wheal, the dye escapes locally and stains the wheal blue The edema fluid, in wheals from all causes, has a high protein content like that of the blood plasma These and other observations support Ebbecke's interpretation that local urticarial lesions result from capillary reactions as described

Ebbecke made the pertinent observation that any agent which will produce a wheal when applied locally in the skin, will produce the syndrome of shock if its effects are induced systemically As examples, he showed that histamine, bacterial toxins, various poisons, "lymphagogues," peptone, proteins to which an individual is sensitive, and other agents will produce a wheal if applied locally The same substances produced shock when injected

[1] Dermographia and wheals are phenomena well known to immunologists and dermatologists The lesions are identical in nature and mechanism Dermographia may be elicited by mild mechanical trauma, as a stroke with a blunt instrument on the skin of a susceptible person Wheals are the characteristic lesions of urticaria They result also from the bites and stings of insects or from injecting into the skin a minute amount of histamine or of a protein to which the individual is sensitive

intravenously Likewise bee sting venom snake venom, bile, cholic salts, emetin allyl formate and various other agents will produce wheals when applied locally and will cause shock when given intravenously It appears that the effects of such agents are due to their action upon capillary endothelium and that the difference between the local and the systemic effects is quantitative rather than qualitative. Wheals are analogous to shock, in that both *result from the same condition—dilatation of capillaries and* increased permeability of the endothelium. *The wheal is shock in miniature*

Lewis made intensive studies on local vascular reactions. These substantiated the interpretations of Ebbecke, that any type of injury to cells—mechanical, thermal electrical chemical or toxic —causes a local reaction which he called the "triple response" This consists of (1) a dull red area, due to capillary dilatation and engorgement followed by (2) a pale elevated area the wheal itself, due to edema resulting from transudation of plasma through abnormal permeable capillary endothelium, and (3) a spreading bright red 'flare' in the surrounding skin, due to local arteriolar dilatation The dull red reaction and the wheal occurred in totally denervated skin and were shown to result from a substance released by cells in response to injury (see Chapter I) The spreading flare occurred only in skin whose sensory nerve fibers were intact. It was attributed to an axon reflex from a sensory nerve fiber to nearby arterioles causing them to dilate.

He showed that this is not caused by the injury itself but by the liberation of substance from the injured cells. The response of the minute vessels to this substance is indistinguishable from their reaction to histamine The capillaries become dilated atonic, engorged and permeable to the plasma. Edema develops in the surrounding tissue, and the capillaries are filled with closely packed corpuscles. Lewis called this *H substance* because its local effects were like those of histamine in all particulars. He believed it to be a single substance and that if it is not histamine itself it is closely related to it.

Lewis saw a direct relationship between the local response of capillaries to the release of H substance and the grave systemic effects resulting from massive effects of the same kind 'These effects lead to an impounding of the blood in the capillary reservoirs accompanied by a serious loss of fluid into the tissue spaces Owing to this diversion of the blood the central vessels are depleted, a profound and lasting fall in blood pressure follows, leading to

a condition of collapse" He stated that the difference between this effect and the "triple response" is one of quantity, not of quality, that the underlying principle is the same the unvarying response of cells to injury, and the effects of H-substance on the endothelium of capillaries and venules

Dale reviewed the observations on vascular skin reactions and stated that there exists no more direct evidence that adrenalin is discharged by the adrenal gland into the circulation than that the H-substance of Lewis, exists as a constituent of normal cells and that it is released as such following mild injury He endorsed Lewis' interpretation of the effects of H-substance on endothelium

Krogh analyzed critically the observations and deduction of the authors mentioned, and endorsed them without qualification "The evidence brought together by Lewis proves, in my opinion definitely, that we have to do in all the acute indirect reactions with a substance released by the injury to tissue cells, and makes it very probable that this substance is closely related to histamine and may be histamine itself,—a conclusion already expressed by Ebbecke" He (p 355) regards it as "proved conclusively that traumatic shock is due to the action of toxic substances formed without the intervention of microorganisms in the injured tissue and distributed throughout the body by the circulating blood itself It is evident now that these substances belong to the class of H-substances" He believes that the circulatory collapse after extensive superficial burns is due to the same mechanism (p 356)

Lindgren studied the distribution of blood in peripheral insufficiency of the circulation occurring after narcosis, surgical operations, trauma, peritonitis, pancreatic necrosis, anaphylaxis and histamine poisoning He found a decreased amount of circulating blood and a diminished plasma volume The capillary portion of the circulation was rich in blood, while the reservoir organs were empty and the larger vessels contained little blood He supports the following thesis

Due to resorption of liberated toxins and products of split albumen, there occurs a general injury to the capillary system which is expressed in dilatation and an increase in the capillary permeability with a secondary discharge of plasma and a loss of liquid from the blood Owing to a generalized capillary dilatation and increased viscosity of the blood, the blood current is retarded in this part of the vascular system Combined with the loss of plasma, this leads to a decrease in the amount of blood returning to the heart This must lead to a decrease in the arterial blood pressure which in turn further impairs the peripheral circulation In this manner one process links up with the other and the result is a progredient insufficiency in the peripheral circulation

TOXIC SUBSTANCES IN THE BLOOD

The explanation of traumatic toxemia has been opposed on two chief grounds It has been emphasized that no toxic substance has been isolated or identified in the blood of man or animals in shock Also that blood either from the general circulation or from the traumatized limb has not been shown to produce a shock like effect in animals receiving such blood by transfusion Because of the importance attached by some writers to these objections, they deserve more than passing mention

It is well known that areas of damaged tissue undergo digestion and absorption The digestion is partly by autolysis, produced by enzymes within the cells, partly by enzymes in the tissue fluids and those supplied by leukocytes—heterolysis Such digestion does not produce a single product of known chemical formula, but rather a series of substances representing intermediate stages of protein cleavage. The science of chemistry has not yet advanced to the stage where these substances can be identified with certainty when mixed with albuminous fluid such as plasma. For example, Witte's peptone is derived by partial digestion of fibrin chemists have shown that it consists of a varying combination of proteoses and other cleavage products. An intravenous injection of Witte's peptone will produce shock promptly but the detection of peptone in the blood might be difficult

Let it be recalled that Vaughan s crude soluble poison, derived by hydrolytic cleavage of various proteins, was found to be more potent than either peptone or histamine. Yet the Vaughans were not able to give chemical data other than that the poison was a product of primary cleavage sufficiently like the original protein that it responded with a positive reaction to Millon s reagent

Those who urge the objection mentioned should be reminded of two pertinent facts (1) The numerous instances on record in which watery extracts and autolysates of various normal tissues have caused shock when introduced parenterally Ebbecke Lewis and others have shown that cytoplasmic substance not subjected to autolysis, evokes endothelial reactions like those caused by histamine (2) The sharp elevation of the non-protein nitrogen in the blood during shock from diverse causes Whipple and others have shown that this is derived from the animal s own tissues and that it indicates proteolysis of the cytoplasm of injured cells An increase in the non-protein nitrogen is about as near as chemical examinations may be expected to approach to the detection of the substances discussed

Inability to demonstrate by chemical analysis or experimentally a toxic substance in the blood during shock, has been interpreted by some as proving the absence of any such a substance A number of investigators (Blalock, Phemister, Freedlander, Holt and McDonald, O'Shaughnessy and Slome and others) have injected or transfused into normal animals varying quantities of blood drawn from animals in shock In other experiments, blood drawn from the veins of traumatized limbs was used similarly Variations of arterial blood pressure were used as criteria of toxic effects In most such experiments no depressor effects were obtained These negative results were urged as evidence of the absence of histamine, or of any other substance having a histamine-like action, as a factor in shock resulting from trauma

Physiologists (see Starling, also Drinker and Field) are in agreement that protein and other colloidal substances are not absorbed from tissues into the blood stream, but that such absorption occur *via* the lymphatics Cytoplasmic substance and products of tissue autolysis are colloids Hence the blood for experiments such as described should be collected from the vena cava proximal to the opening of the thoracic duct or from the pulmonary arteries No such experiments have been reported However, it is probable that, even under these conditions, no intoxication would be seen in the animals which received the blood Shock developing after extensive trauma or burns, independent of hemorrhage and anesthesia, is a gradual affair extending over many hours It is not probable that any effective quantity of the substances in question would be contained in the entire volume of the animal's blood at any one time

Evidence based on failure to show toxic effects by transfusion, is entirely negative in character and is therefore inconclusive and untrustworthy Similar results would probably be obtained if such experiments were made on dogs which had been bitten by venomous snakes If understanding of the mechanism by which a snake bite produces death, had depended on showing the presence of an intoxicating amount of venom in the bitten animal's blood, such understanding might still be a matter of inference or conjecture

Indeed, a clever logician could frame a theory concerning the effects of snake bite, which might deceive the uncritical Not only the area about the bite but the entire limb swells rapidly and extensively The tissues become markedly distended with hemorrhagic edema fluid The minute vessels are greatly engorged and

there is diffuse hemorrhage from the dissolution of vascular walls. These observations indicate that death from the bite of a venomous reptile can be explained on the basis of local loss of blood and fluid in the injured area without resort to the supposition that a poisonous substance absorbed from the bitten area exerted a systemic toxic effect. In support of this theory, it is urged that no poisonous substance has yet been isolated and identified as such in the blood of animals or man after snake bite.

"But," observes some critical reader, "The injection of snake venom intravenously or otherwise will cause the same signs of illness often ending fatally as those resulting from a snake bite Pharmacologic evidence indicates that venom produces systemic as well as local effects.' Quite true, but should not that same logic apply also to the effects of extracts of normal tissues and of substances resulting from proteolysis? Instances of such effects are presented in the subsequent chapter

Referring again to experiments by transfusion in a few significant instances shock like phenomena are recorded in investigations using this method Cornioley and Kotzareff produced shock in guinea pigs and rabbits by traumatizing the limbs with repeated light blows from a small hammer They then injected the blood from these into normal anaimals of the same species. A state of shock developed in 6 guinea pigs and 2 rabbits so treated In another series the serum from the entire blood volume obtained from a guinea pig in shock was injected into the peritoneal cavity of a normal guinea pig Fatal shock was reported in 8 such trials Postmortem examinations showed marked pulmonary hyperemia and petechial hemorrhages in the lungs and liver

McIvers and Haggard joined the posterior half of one cat with the anterior half of another by vascular anastomoses Shock produced by trauma to the limbs of the one caused a marked fall in blood pressure in the untraumatized cat in several such experiments.

Kendrick, Essex and Helmholz made a more precise experiment of a similar kind eliminating sources of error presented by direct vascular anastomoses. A heart lung limb preparation was made on a dog under nembutal anesthesia. The aorta was canulated and all other structures below the first lumbar vertebra were severed from the anterior part of the body Blood from the vena cava was either returned to the reservoir of the heart lung limb preparation or was used for transfusion to a normal dog the recipient Each time a transfusion of a carefully measured quan

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tity of blood was given to the recipient, an equal quantity of his blood was withdrawn and added to the reservoir of the heart-lung-limb dog This prevented any significant changes in the total blood volume of either dog Exchanges of 100 cc quantities were made at intervals of about ten minutes during the experiment After both dogs had been prepared, the thigh muscles of the heart-lung-limb dog were traumatized

> Blood from unaffected limbs or from limbs traumatized for short periods did not produce shock in the recipients as determined by blood pressure and the concentration of hemoglobin during the period of observation Blood from limbs traumatized for thirty-five to forty minutes caused a significant decrease in blood pressure within forty minutes after the first exchange of blood and death a few hours thereafter It is concluded that the results of the experiments described in this report furnish suggestive, but not conclusive, evidence for the toxemia theory of shock

Best and Solandt reported results of experiments arranged by connecting a rotary exchange transfusion pump between the vessels of 2 heparinized dogs This apparatus maintained a continuous exchange of exactly equal volumes of blood between the circulations of the two animals The exchange of blood, prior to the onset of shock, had no effect on the blood pressure of either animal Using a technique for producing trauma with little or no hemorrhage, they produced profound shock with insignificant fluid loss at the site of injury, and the arterial blood pressures of both dogs declined at approximately equal rates They interpreted this as indicating the effect of a shock-producing agent conveyed by the blood They concluded that there is a factor in the production of shock, which acts on tissues which have not been directly affected by mechanical injury They found evidence suggesting "that a toxic substance or substances released from injured tissues may play a rôle in the production of traumatic shock " Attempts to identify these substances chemically were not successful

Recently (1941) Freeman, Cullen and Schecter produced shock in sympathectomized dogs by numerous light blows with a small hammer The limbs had been bandaged and taped to prevent local extravasations of blood and fluid An adequate circulation was maintained as indicated by a normal peripheral blood flow, sustained blood pressure and a normal oxygen saturation of venous blood Even under these circumstances traumatic shock could be produced in totally sympathectomized dogs Characteristic pathologic changes occurred in the viscera and the blood volume,

as determined by the carbon monoxide method, was reduced by more than could be accounted for by the local loss into the area of injury They believe that this loss of blood volume may well be explained on the basis of a toxic factor absorbed from the trauma tized region

Summary —The reports of The Special Committee on Shock and Allied Conditions indicated that shock in wounded men results from a combination of causes including exhaustion exposure, pain, anxiety hemorrhage infection, and the absorption of products of tissue autolysis from the area of injury The latter was regarded as the most important of these factors.

This explanation originated from observations on all types of battle casualties and it received confirmation from experimental studies The theory integrates neatly with the principles of endothelial function and capillary reactions and it was endorsed by eminent students of circulatory physiology

It is significant that several workers who formerly opposed the theory of toxemia recently have produced evidence supporting this explanation

The fact that extracts of normal tissues metabolites and products of proteolysis will produce shock when introduced parenterally likewise supports the conception of traumatic toxemia Several instances of these effects will now be cited

CHAPTER VII

CIRCULATORY EFFECTS OF TISSUE SUBSTANCES

MANY observations on the circulatory effects of tissue extracts, proteins, protein-split products and metabolites, have been recorded These become understandable when considered in relationship to the capillary reactions previously discussed Increased flow of lymph as resulting from damage to endothelium was explained in Chapter I Heidenhain's observation of a fall in blood pressure accompanied by increased concentration of the blood as a characteristic effect of his "lymphagogues," is highly significant because of its relationship to endothelial damage Intravenous injections of various proteins and products of protein cleavage produce an increased flow of lymph and, if large doses are given, immediate death by circulatory failure may result The interpretations of Ebbecke, Krogh, Dale and Lewis, mentioned in the preceding chapter, make such circulatory effects more intelligible It is pertinent to review some of those observations before considering other proposed explanations for shock

Richet (1906) described the severe illness, circulatory collapse and death which resulted from injecting extracts of actinia and of other marine animals into dogs

> Shortly after the toxic dose has been injected intravenously the dog is seized with intense vomiting and diarrhea The prostration is almost immediate The animal lies down and breathes with difficulty However there are no marked cardiac phenomena That which dominates the scene is the violent abdominal distress with diarrhea, intestinal hemorrhages which sometimes are profuse, rectal tenesmus and in severe cases hypothermia The vomitus usually contains blood At autopsy one finds a diffuse exudation of blood in the mucosa of the stomach and of the entire intestinal canal throughout its length Frequently there are hemorrhages in the peritoneal and endocardial surfaces

The visible effects upon the minute vessels in the viscera were so marked that Richet coined the term *congestin* to indicate the toxic substance which produced them

Hamburger found that filtrates of various bacterial growths caused an increased flow of lymph It is well known that these will cause death by circulatory failure if given intravenously in sufficient dosage

Asher showed that bile, bile salts and foreign sera cause an

increased flow of lymph when given intravenously to dogs Bile or its salts will produce varying degrees of shock if injected intra venously, intraperitoneally or subcutaneously into dogs (Horrall and Carlson, Harmon, Harkins *et al*) Moon and Morgan produced shock ending in death at intervals varying from a few minutes to a few days by injecting varying doses of bile or of sodium glycocholate The blood of these dogs became markedly concentrated after the injections, and the viscera at postmortem examination showed the changes characteristic of shock

Chittenden, Mendel and Henderson injected proteoses, peptones albumoses and other products of the partial digestion of protein into dogs A decline in blood pressure, delayed coagulability of blood and an increased flow of lymph were the results. The lymph contained an increased percentage of protein and was reddish in color because of erythrocytes which it contained.

Vaughan produced a crude poison by hydrolytic cleavage of various proteins Minute quantities of this, given to animals intravenously, caused severe illness which often ended in death by circulatory failure Underhill and Ringer compared the effects of this poison on animals with the effects of peptone and of hista mine It was found that each caused an immediate decline in blood pressure accompanied by hemoconcentration The effects of Vaughan s crude poison were more severe than those of either peptone or histamine

Dale and Laidlaw (1911–12) found that small doses of histamine caused a marked increase in the flow of lymph in dogs. Later (1918) they showed that larger doses produce circulatory failure, not cardiac nor vasomotor in origin, associated with a fall in blood pressure The total blood volume was reduced and the plasma volume was decreased as shown by red cell count, hemoglobin content and hematocrit readings. The authors saw a direct relationship between the mechanism of peptone poisoning, of anaphylactic shock and the effects of histamine They regarded the action of histamine as typifying the effects of a large class of substances including bacteria and their products extracts of various tissues foreign sera and other proteins peptone and other products of protein cleavage As they saw it, the similarity between these unrelated substances lay in the fact that they have one property in common that of injuring capillary endothelium The central feature of the systemic effects of these agents is oli gemia resulting from capillary atony leakage of plasma and consequent hemoconcentration

Dale (1935) stated definitely that shock following trauma is not due to histamine poisoning but he adhered to the original explanation that other substances absorbed from injured tissues gradually induce capillary permeability resulting in effects *like those of histamine* He warned against accepting too readily the evidence indicating that shock is due solely to loss of blood and fluid in the traumatized areas "I do not think that the evidence yet advanced entitles us to rule out some form of toxemia in some kinds of shock "

Turck (1897) showed experimentally that products of disintegrating tissues are poisonous when injected into animals, and believed that wound shock is due to toxic products absorbed from damaged tissues Schafer and Moore (1896) found that the intravenous injections of extracts of brain substance is followed by a marked fall in blood pressure Vincent and Sheen (1903) confirmed that report, the intravenous injection into cats of 5 cc of such extracts caused a fall in blood pressure accompanied by an increased volume of an intestinal loop and of the leg, as shown plethysmographically Increased volume of tissues results from an increased amount of blood or fluid in the part affected, and indicates a circulatory disturbance They produced similar results with extracts of striated, non-striated and cardiac muscle, kidney, liver, spleen, testes, ovary, pancreas and lung They believed that the depressor effects resulted from the direct action of these substances upon the blood vessels and concluded that extracts of normal tissues lower the blood pressure by causing vascular dilatation Carlson, Woelfel and Powell (1908) reported exactly similar results from experiments of this kind Injections of extracts of pancreas, salivary gland, gastro-intestinal mucosa, liver, spleen, kidney, lung, testis, thymus, thyroid and muscle were found to produce depressor effects in varying degrees

Popielski (1909) gave extracts of intestinal mucosa to dogs by intravenous injection These produced a sudden marked fall in blood pressure accompanied by acute illness, vomiting, urination, liquid defecations, salivation, weakness and collapse If death did not follow, these disturbances disappeared as the blood pressure returned to normal Similar effects followed injections of extracts of brain, cord, pancreas and of erythrocytes He commented on the fact that the blood of animals, after injections of tissue extracts, became incoagulable In one instance, blood drawn from an artery remained unclotted for sixty-four hours He attributed these effects to "vaso-dilatin" which he showed to

be a constituent of normal cells In order to obtain it the cells must be mechanically injured, mashed or lacerated uninjured cells would not yield it. These observations are of particular significance in the light of the subsequent work of Ebbecke and of Lewis described in the preceding chapter Perret reported that "myoserum," the juice pressed out of muscle, produced highly toxic effects when injected

Miller and Miller reviewed many preceding reports on the effects of organ extracts and recorded their own results with saline extracts of parathyroid, thymus, brain, cord, liver kidney, spleen pancreas, prostate, ovary and testis. Extracts of spleen raised the blood pressure the others invariably caused a fall in blood pressure when injected Alcoholic extracts of most tissues had no such effect, excepting those of brain and cord, these caused the pressure to fall Fawcett, Rogers, Rake and Beebe extracted normal tissues and removed the coagulable proteins from the extracts by precipitation The tissues so treated were liver thyroid spleen, thymus, pancreas muscle and others The injection of extracts so prepared caused an immediate fall in the blood pressure and an increase in the pulse rate

Stone, Whipple and Bernheim made aqueous extracts of the mucosa of strangulated loops of bowel The intravenous injection of such extracts caused immediate illness shown by vomiting defecation, urination, and profound prostration The vomitus, feces and urine contained blood, the blood pressure declined rapidly and death by circulatory failure resulted No erythrocytic counts nor hemoglobin estimations were reported The post mortem findings were identical to those later shown to be characteristic of shock. The authors attributed these effects to toxic substances contained in the damaged mucosa

Delbet and Karajonopoulos made a sterile autolysate of rat muscle The intraperitoneal injection of this into rats caused marked illness and death Out of 22 rats so treated, 14 died within an hour and 6 in from four to twenty hours

Cornioley and Kotzareff traumatized the muscles of guinea pigs and rabbits by methods similar to those used by Cannon and Bayliss These injuries caused symptoms of shock usually ending in death in a few hours Shock was delayed or prevented by placing a tourniquet around the limb above the traumatized area or by amputation of the injured parts. Extracts of the traumatized tissues caused evidences of shock in normal animals when injected intravenously

Phemister and Handy found that normal erythrocytes, traumatized by shaking, give origin to a vaso-dilator substance The transfusion of these into normal animals of the same species caused marked vaso-dilatation and a decline in blood pressure Similar transfusions of non-traumatized blood had no such effects Injections of laked blood produced effects like those of traumatized red cells Gesse reported similar results from injections of hemolysed blood

Wangensteen and Waldron tested the effects of autolysed tissues by placing portions of liver, pancreas, spleen and intestine in the peritoneal cavities of dogs In other experiments they first sterilized the tissues then allowed them to autolyse for varying periods *in vitro* The injection of sterile products of autolysis caused degrees of illness varying from immediate death, delayed death to recovery Chemical examination showed a decrease in the blood chlorides and an increase in the non-protein nitrogen of the dogs treated by autolysis *in vivo*

Mason and his collaborators found that the autolysis of normal liver substance *in vivo* produced marked intoxication, loss of blood volume and death in dogs In these experiments a small portion of liver was clamped, excised, weighed and dropped back into the peritoneal cavity of the same animals Death followed regularly in fifteen to twenty hours They attributed this to toxic substances derived by autolysis of liver substance Andrews and his associates repeated Mason's experiments and verified his results They found also that bits of liver implanted in the chest or subcutaneously produced intoxication and death In a later report Mason and Lemon occluded the blood supply to a portion of the liver in dogs These animals developed low blood pressure and died in fifteen to eighteen hours They allowed liver substance to undergo autolysis *in vitro* and injected the autolysate into normal dogs Small doses caused a rise in blood pressure while larger doses caused an opposite effect Doses of 7 or 8 cc were usually fatal and an injection of 10 cc caused immediate death by shock

Blalock's results from one group of experiments are similar in character to those quoted He obtained fluid from the normal and from the traumatized tissues of dogs in which shock had been produced by bruising the muscles Fluid from non-traumatized extremities was injected into 5 dogs In 4 of these there was a marked decline in the blood pressure during or immediately after the injection One of these died five hours later It was believed

that the others would have recovered if they had been allowed to live Fluid obtained from traumatized tissues was injected intravenously into 9 dogs Eight of these died at periods varying from a few minutes to twenty four hours after the injections.

These findings are highly significant in view of Blalock's contention that shock is due to loss of blood and fluid at the site of the trauma Blalock's sole criterion for shock was a decline in arterial blood pressure Judged by this criterion, these dogs died of shock produced by the injection of fluids from normal and from traumatized tissues *without local loss of blood or fluid*

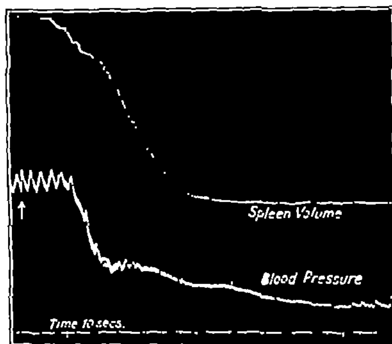


FIG. 4 —A record of the blood pressure and splenic volume of a dog Ten cc. of a watery extract of mucosa from a strangulated loop of bowel (indicated by arrow) caused a sudden fall in blood pressure accompanied by a marked contraction of the spleen as it discharged its reservoir blood into the systemic circulation.

Moon and Kennedy produced shock in dogs by introducing fresh finely chopped dog muscle into the peritoneal cavities of normal dogs by injecting fat free neutralized watery extracts of muscle intraperitoneally, by intravenous injections of the same, and by intraperitoneal or intravenous injections of autolysate of dog muscle In later experiments watery extracts of intestinal mucosa, from normal areas and from the lining of obstructed loops of bowel were shown to have similar effects (see Fig 4) In each instance these caused the evidences of illness usually seen in shock hemoconcentration, and the postmortem findings were

those regularly present after death by shock in animals and in man A detailed discussion of the latter is given in Chapter XI

Coonse and his collaborators compared the effects of trauma and of hemorrhages upon healthy dogs of a similar type and size Repeated trauma was made upon the muscles of the legs until the blood pressure sank to the critical level The traumatized muscle together with its blood and fluid was finely chopped and extracted with saline solution The injection of this caused illness, low blood pressure, hemoconcentration and other evidences of shock Hematocrit readings and blood counts showed hemoconcentration after trauma, but following hemorrhage the opposite picture of hemodilution appeared They differentiated shock from hemorrhage by this test and by the presence of marked acidosis in shock and the absence of it after hemorrhage They stated that the postmortem findings resembled in every particular those described by Moon and Kennedy The large veins and heart contained only a small amount of blood There was marked congestion of the small vessels in the viscera The blood was dark, thick, viscid and slow to clot The tissues after death from hemorrhage showed the pallor which is characteristic of exsanguination

Konig made extracts of fresh, finely ground rabbit muscle in saline solution These, after filtration and centrifugation, were given by intravenous injection to rabbits One cc of the filtrate caused signs of collapse and a decline in the arterial pressure of 40 to 60 mm of mercury The injection of 2 cc caused fatal shock He noted that muscle extract which has stood thirty to sixty minutes lost much of its toxic properties Konig believed these experiments illustrated the mechanism of shock resulting from extensive injury to muscle These experiments were repeated and the results and interpretations confirmed by Schorcher He recorded congestion of the viscera after such injections

Pressor and Depressor Effects.—Many investigators have confirmed the observation that extracts of various tissues will disturb the circulation if given intravenously Much discussion arose over the observation that in some experiments the blood pressure rose while in others it declined Attempts were made to explain this on the supposition that extracts of tissues contained both *pressor* and *depressor* substances Later it was shown, as in the experiments of Mason and Lemon, that an extract caused a *rise* in pressure if given in *small dosage*, while *larger doses* of the same extract caused the pressure *to decline* Hence the differentiation into pressor and depressor substances was not valid

Crile studied the circulatory effects of various forms of trauma

on dogs The earliest circulatory effect was a *rise* in the arterial pressure which subsequently declined as circulatory failure developed Numerous other workers have shown that various forms of tissue abuse produce an initial rise in arterial pressure The decline in pressure would occur later when the effects of the tissue abuse became more pronounced

Both these phenomena are explainable as the action of the mechanism of compensation previously discussed The earliest effects, either of tissue extracts or of trauma, upon the circulation bring the compensatory mechanism into action Activity of the sympatho-adrenal system results in stimulation to the heart arterial vaso-constriction contraction of the spleen and the discharge of its reserve volume of blood into the circulation These effects cause the arterial pressure to *rise*, it falls only when the compensation is no longer adequate That effect may result when large doses of an extract of tissue or other injurious agent is given, or when the effects of tissue abuse are no longer compensated

Summary —It appears that many substances derived from animal tissues, including aqueous extracts, proteoses, peptone, other products of protein cleavage and extracts of various marine animals, also bacterial protein and products of bacterial metabolism, histamine, bile and its salts produce circulatory disturbances accompanied by hemoconcentration, low blood pressure and other shock like manifestations when introduced into the blood stream Products of the autolysis of normal tissues *in vivo* affect the circulation in a similar fashion

Apparently the substances mentioned, and others whose action is similar produce their effects by increasing the permeability of capillary endothelium The resulting disturbances of the circulation depend in part upon the degree and extent of this effect upon endothelium

Whether such substances cause a transient increase or a decline in the blood pressure depends largely upon the dosage When the effects of small doses are completely compensated the blood pressure may rise Larger doses for which the compensation is inadequate cause the pressure to decline

An understanding of capillary reactions makes intelligible the phenomena discussed in this chapter The observations cited appear to integrate smoothly with the pathologic physiology of endothelium also they support the conclusions of the Committee on Wound Shock and Allied Conditions as summarized in the preceding chapter

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In considering the significance of these and of other similar experiments, the effects of uncomplicated hemorrhages in dogs are pertinent. Milroy showed that animals will restore the blood to its normal volume spontaneously in a few hours after losses of more than one third of the total blood volume Roome Keith and Phemister showed that the volume of hemorrhage necessary to cause death if occurring within one hour in anesthetized dogs, was 58 6 per cent of the total blood volume if bled more slowly, 70 per cent of the blood volume was required Swingle and his associates found that an unanesthetized dog recovered spontaneously after withdrawing blood amounting to 4 5 per cent of the body weight within fifteen minutes Spontaneous recovery followed the more gradual withdrawal of blood amounting to 5.5 per cent of the body weight, *i e*, about 75 per cent of the total blood volume. Estimated losses of blood and fluid comparable to these, have not been reported as resulting from experimental trauma.

Evidence of redistribution of fluids after either trauma or hemorrhage was shown in another series of experiments by Blalock and his collaborators. The tissues about the injury had an increased content of water and those elsewhere, particularly the muscles, had lost water This redistribution of fluids is highly important and constitutes an unrecognized source of error (p 90)

The authors found no evidence of shock following the release of the obstructed circulation from traumatized areas. They injected fluid from normal and from traumatized limbs into normal dogs A prompt decline in the blood pressure, usually ending in death, was the result (see p 82) The apparent significance of this finding as indicating a condition of shock in these dogs, was disregarded They saw no evidence indicating the absorption of substances from traumatized tissues which would affect the circulation systemically and concluded that shock can be explained satisfactorily as resulting from loss of blood and fluid at the site of the trauma.

Similar studies were made on shock produced by burns and by manipulation of the intestines They believed that the fluid lost in and about burned areas, and that lost from the peritoneal membranes after manipulation was sufficient to explain the circulatory failure in these conditions, independent of the absorption of injurious substances from damaged tissues. However, Blalock stated in a subsequent article that when death occurs

twenty-four hours or longer after burns, the absorption of toxic substances is probably a factor

Phemister and his associates performed several groups of experiments similar in character and in results to those of Blalock Venous blood returning from traumatized limbs was collected and transfused into normal dogs This did not produce evidences of circulatory disturbance in them He concluded that if there are vasodilator substances in blood from traumatized limbs, they are not in sufficient quantities to be detected by this method

At necropsy examination the limbs of dogs, in which shock was produced by trauma, showed voluminous hemorrhage sufficient to account for the fall in blood pressure It was stated that the estimated loss of blood by trauma was sufficient in amount to produce death if withdrawn in the course of an hour

The effects of crushing injuries to nerves accompanied by prolonged faradic stimulation were observed They were unable to produce manifestations of shock by these methods The effects of trauma upon denervated limbs were compared with those of trauma to limbs with intact nerves, the development of shock was not retarded nor prevented by severing the nerves No increased decline of the blood pressure resulted from the massage of traumatized limbs Obstruction to the circulation by tourniquet, or by ligature of the vessels leading to the injured area, did not result in a fall in blood pressure when released They found no evidence indicating absorption of injurious substances from the areas of injury

The weights of traumatized limbs were compared with those of the corresponding untraumatized limbs, following the method used by Blalock The increase in weight of traumatized legs ranged from 310 gm in a dog weighing 7 kg to 1057 gm in one of 20 kg weight The average increased weight of traumatized limbs in 38 such experiments was estimated as sufficient to cause death by hemorrhage in dogs of similar size Hemoglobin estimations and erythrocyte counts showed regularly a decrease in the concentration of blood, in no instance was hemococentration recorded This was in contrast to their finding of hemoconcentration after injections of histamine

The necropsy findings were those characteristic of death by hemorrhage The heart and vessels contained little blood, and the mucous and serous surfaces were pale The traumatized muscles contained extensive extravasations of blood which infiltrated the septa and formed large collections in those areas.

Numerous vessels small and large were found torn They concluded that the predominant factor in these experiments was hemorrhage into the damaged tissues They failed to demonstrate the presence of any toxic substance originating in the areas of injury and attributed the circulatory failure to local hemorrhage not to traumatic toxemia

In view of the losses of blood up to 1057 gm in amount, the hemodilution which developed, the recovery following transfusion, the anemic condition of the viscera and the massive hemorrhages in the traumatized areas one must concur heartily in their conclusions Whatever effects may have resulted from absorption of substances from injured tissues, were entirely overshadowed by the effects of hemorrhage The experiments were not such as to make possible a distinction between the effects of trauma and those of hemorrhage Confusion between the effects of trauma and hemorrhage absorption of tissue proteins and other factors combined in such experiments, will be discussed presently (pp 110–113)

Roome Keith and Phemister compared the effects of hemorrhage with the conditions resulting from trauma in dogs The volume of blood necessary to cause death, if withdrawn within an hour ranged between 34 per cent and 82 per cent of the estimated blood volume The average amount was 58 6 per cent of the blood volume They found hemodilution after hemorrhage and hemoconcentration in shock produced by manipulation of the intestines but after trauma to the muscles they found the blood diluted This observation and the finding of massive extravasations in the traumatized limbs indicate that hemorrhage was a major factor in the resulting circulatory failure They concluded that the low pressure developing after injections of histamine in anaphylaxis and after section of the spinal cord resulted from dilatation of the minute vessels but the effects of trauma and of intestinal manipulation were attributed to local loss of fluid rather than to toxemia.

Harkins and Hudson produced shock by freezing one side of a dog s body with solidified CO_2 This was followed by a marked fall in the blood pressure and by hemoconcentration They found increased fluid in the frozen side amounting to 2 55 per cent of the body weight and believed that this amount of plasma, if lost from the blood stream was sufficient to account for a large part of the shock present in these animals

Harkins made similar observations on shock produced by burning Dogs were held rigidly in a plaster paris cast and placed on

a balanced tipping apparatus which recorded lateral shifts of weight kymographically The dogs had been anesthetized with barbital One side of the animal was then burned with a Bunsen flame applied through openings in the plaster cage An immediate shift of weight to the burned side occurred Hemoconcentration developed early but the blood pressure did not decline until shortly before death, which occurred 1 5 to 6 5 hours after the burns The bodies were then bisected longitudinally for comparison of weights The burned side outweighed the other by 1 5 per cent to 3 1 per cent of the total body weight The author concluded that the accumulation of fluid about the burned area is of importance and places the reaction in the category of secondary shock The inference is left to the reader that the circulatory failure was due to the local loss of fluid

Comparisons of the weight of injured and non-injured halves of the body include a factor of error which was not taken into account When fluid is lost from the blood, by hemorrhage or otherwise, fluid is simultaneously absorbed from normal tissues to replace that lost This is part of the physiologic mechanism by which blood volume is maintained The injured tissues gain in weight at the expense of those not injured and the latter tend to become dehydrated This redistribution of fluid was shown by Blalock and by several other workers Suppose 100 gm of fluid were so shifted the difference in weight of the two sides would then be 200 gm , but the *actual gain* of the affected side would be only 100 gm The *difference in weight* includes *twice* the volume of fluid shifted by dehydration and redistribution, and such experiments provide no means for determining what amount of fluid is thus shifted This factor of error, multiplied by 2, occurs in all such computations

In defense against this objection, Harkins stated that not more than one-sixth of the dog's total tissue had been damaged, hence the factor of error was reduced to negligible proportions None the less, one repeats the observation that no shifting of fluid from one part to another *of the burned side*, would increase the total weight of that side A gain in weight of that side indicates *per se* that the fluid came from elsewhere The difference represents *twice* the volume of fluid shifted from the *normal* to the *injured* side This factor of error seems to deserve consideration

Roome and Wilson obtained fluid from traumatized muscle under great pressure in a hydraulic press Sudden death followed the intravenous injection of such fluid in each of 6 dogs

Muscle juice and fluid, obtained in the same manner, but freed from sediment and fat by centrifugation, was injected into 3 heparinized dogs This resulted in an increased blood pressure in 2 and a decrease in 1 Muscle extract, injected into the same dog from which the extract was derived, caused the blood pressure to decline Muscle juice, combined with a bloody fluid from the traumatized tissues, caused a moderate increase of blood pressure in each of 5 dogs The injection of bloody fluid alone caused a slight rise of blood pressure in 4 dogs and no pressure effects in 2 The injection of muscle juice alone caused a fall in blood pressure in 5 dogs and no pressure change in 1 In each instance the variations in pressure were transient

The amount of extract given to 1 dog was stated, but no other data as to dosage were given Small doses of tissue extracts may cause an increased blood pressure, while larger amounts cause the pressure to fall The dosage given would seem to be important in such experiments The bearing of the recorded results upon the mechanism of shock is ambiguous their maximum apparent significance is that they confirm the observations discussed in the preceding chapter Extracts of tissues may produce either pressor or depressor effects, depending partly on dosage and partly on the method of extraction Notwithstanding the varying results of these experiments, the authors interpreted them as invalidating the theory of traumatic toxemia.

Freedlander and Lenhart repeated and confirmed the experiments of Blalock. They concluded that shock resulting from trauma can be explained as due to hemorrhage and to local loss of fluid Holt and Macdonald performed a series of experiments by the same technique Shock was induced by severe repeated trauma to the limbs of animals under barbital anesthesia. The gain in weight of the traumatized limbs, was considered sufficient to account for the collapse and made it unnecessary to assume the absorption and general action of any histamine like substance The transfusion of blood from traumatized limbs into normal animals showed no evidence of a depressor substance in the blood

A few other reports might be cited, but all the workers used similar methods and drew similar conclusions from the results. These agreed that no effects on the systemic circulation could be demonstrated as resulting from the absorption of toxic products from the areas of injury, and that all the manifestations of traumatic shock may be explained satisfactorily by the loss of blood and/or fluid locally at the site of the injury

Factors of error inherent in the technique used in these and in other series of experiments, will be discussed in a subsequent chapter These sources of error must be considered before passing judgment on the validity of the proposed explanation and of the authors' conclusions

Nociceptive Nerve Impulses.—This theory is based upon the supposition that nerve impulses originating in traumatized areas, operate in some manner to cause a progressive deficiency of the circulation It, in a sense, reaffirms part of the logic which supported Crile's first conception of shock

O'Shaughnessy and Slome made several types of experiments on trauma, transfusions and amputations performed on animals under general anesthesia, using variations in blood pressure as a criterion of the effects Blood drawn from the veins of traumatized limbs, did not cause shock when given to normal dogs by transfusion

An apparatus was designed consisting of a small chamber divided into 2 compartments by a membrane for dialysis This was connected with the vessels of 2 dogs in such way that substances might pass by dialysis through the membrane from the blood of one into that of the other One of the dogs was then traumatized and immediately his blood pressure declined rapidly, ending in death within thirty minutes There was no evidence of a depressor substance conveyed by dialysis into the blood of the untraumatized dog

They established a crossed circulation, both arterial and venous, between the hind leg of animal A and the systemic circulation of animal B That leg of animal A was then traumatized, animal A developed low blood pressure and died but animal B, which supplied all the circulation to the traumatized limb, was not affected This was regarded as final evidence invalidating the supposition that absorption of toxic substances is a causative factor in shock resulting from trauma The authors concluded that toxemia, due to histamine or to any other depressor substance, is not a factor in the mechanism of traumatic shock They regarded the loss of blood and fluid locally and the discharge of nociceptive nerve stimuli as the important causes for traumatic shock

A few features of these experiments deserve critical examination Traumatic shock caused by injury to muscles alone, seldom develops within four hours after the injury Death within thirty minutes indicates the effects of other agencies The authors assume that substances resulting from trauma to tissues are

dialysable and that they are absorbed into the blood Physiologists teach that such substances are colloidal in nature and are therefore undialyzable also that they are not absorbed from the tissues into the *blood* but *via* the *lymphatics* Overlooking both these objections, one would wish the experiments to be of longer duration than any of those recorded

The authors compared the gross and microscopic appearances of the viscera after death in their traumatized animals with those seen after histamine shock They described marked hyperemia, edema and capillary hemorrhages after death by histamine These features were present in less marked degree in the viscera of traumatized animals One must agree with them that this finding indicated the effects of hemorrhage in the latter It *appears that the data in all such experiments represent the combined* effects of anesthesia, hemorrhage and trauma as discussed on pp 110–113

'Toxemia having been eliminated as a causal factor we were left with two remaining factors—fluid loss at the site of the trauma and the production of nerve impulses in that area.' They measured the local fluid loss in traumatized tissues and found it inadequate to account for more than a minor part of the animals condition Amputation of the traumatized limb from an animal in shock was followed by a marked improvement in the animal s condition Toxemia having been obviated as a factor *in shock this effect indicated that amputation interrupted the* barrage of nerve impulses which if continued would have led to shock

Blood transfusions equal in amount to the volume of fluid lost locally in traumatized limbs, produced only temporary benefit The blood pressure rose immediately to the pre traumatic level, then declined progressively This result indicated to the authors that local loss of fluid was only a minor factor and that the effects of the continuous barrage of nociceptive nerve impulses was the major etiologic agent.

They made oscillographic records of impulses passing over *nerve trunks before during and after trauma.* These were given as conclusive evidence that a barrage of nerve impulses develops as a result of trauma and continues for hours thereafter They secured no evidence as to how this barrage operates to cause circulatory failure but regarded this factor as fundamental to an understanding of the etiology of traumatic shock

Cressman and Benz undertook to verify the observations

described on nerve impulses after trauma, and to determine whether these probably were causative agents in shock Nerve action potentials were amplified and recorded by an oscillograph No consistent barrage of impulses was shown under the same experimental conditions employed by O'Shaughnessy and Slome Increased nerve impulses were recorded from both traumatized and intact limbs

In previous discussions the results of many workers were cited indicating that prolonged stimulation of peripheral nerves will not cause manifestations of shock (205, 265, 306, 325, 361) Also that complete anesthesia prevents sensory impulses, originating in the periphery, from reaching the brain (37, 68), and that shock is not prevented by severing all nerve paths between the traumatized limbs and the brain (30, 31, 141*a*) It has been shown (168, 288[16], 415) that roentgen irradiation of the abdomen causes the complete syndrome of shock This type of injury is entirely painless, hence it would not cause noxious nerve impulses These observations weigh against the theory that nociceptive nerve impulses are important factors in the dynamics of shock

Hyperpotassemia —Scudder's recent work lays emphasis on the increased potassium content of the blood which occurs incident to shock He sees a relationship between this and the fact that certain unicellular marine animals will die if the potassium content of the surrounding fluid is raised to the level of the normal potassium content present within those cells He draws an analogy between this and the development of shock but does not suggest the mechanism by which the hyperpotassemia occurs

The fact, shown by his data, that hemoconcentration regularly *precedes* the hyperpotassemia indicates that the latter is not a primary causative agent but is more probably one of the group of associated disturbances of physiology Alterations in the concentration of potassium and of other electrolytes were discussed in Chapter III, and it was shown that such changes result when living cells are injured from any cause, including anoxia Scudder does not state that shock is due to potassium poisoning, but believes that the alterations in the potassium content of the bloody fluids "serve as a measure of profound cellular changes" What those changes are and how they occur is not set forth

Emphasis on hyperpotassemia as a feature probably will not aid materially in either the theoretic or the practical aspects of the subject It appears that the increased potassium content of the blood is not a causative factor, but one of the resulting dis-

turbances The technical difficulty of making accurate determinations for potassium in body fluids makes it unlikely that this measure will be adopted in hospital laboratories for clinical purposes ✓

The Alarm Reaction —Selye called attention to the syndrome which appears when severe injury is inflicted upon the animal organism. This syndrome is independent of the nature of the damaging agent and represents a response to damage as such Exposure to cold, traumatic injuries, excessive muscular exercise, spinal shock, anaphylaxis, acute infections and intoxications with various drugs will evoke this syndrome, which is interpreted as an expression of general defense He explains shock as inadequacy of the physiologic reactions by which the effects of various injuries are counteracted

The term *alarm reaction* is applied to the sum total of the biologic phenomena elicited by the sudden effects of damaging agents. It represents a "call to arms of all the resources which tend toward adaptation or defense Shock itself is defined as a condition of suddenly developing intense systemic (general) damage and is described as occurring in two phases, *shock* and *counter shock*

The first phase includes tachycardia, a decrease in muscular tonus and body temperature hemoconcentration, transient rise followed by decline in blood pressure, anuria high non-protein nitrogen, acidosis, high potassium and phosphate content, a decrease in the blood chlorides and blood sugar, leukopenia followed by leukocytosis, low basal metabolism, and the discharge of adrenalin from the adrenal medulla. The accompanying tissue changes include visceral congestion edema, effusions, gastrointestinal erosions and acute degeneration of parenchymatous organs. This phase is interpreted as one of relative adrenal insufficiency It may last a few minutes or twenty four hours depending on the degree of the damage Death may follow if the degree of adaptability is limited, *i e* if the defensive resources are inadequate to counteract the damage

If the first phase does not end fatally, it is followed by the second phase—that of counter shock—consisting of a reversal of most of the items mentioned There are hyperplasia and hyper activity of the adrenal cortex, hemodilution increased blood sugar and blood chlorides decreased potassium and phosphates alkalosis diuresis increased metabolism and a rise in blood pressure and in body temperature

This conception omits essential parts of the problem from consideration Others have studied the *mechanism* by which damaging agents disturb normal functions, Selye has focused attention on the physiologic resources for *counteracting the damage* The former say the animal dies from the systemic effects of the damage, the latter attributes death to inadequacy of the defensive reactions Obviously, interest should not be limited to the dynamics of the injury but should include also the counteractive mechanisms However, shock interpreted as inadequacy of the physiologic defenses presents an uncompleted picture One still would inquire by what mechanism are the circulation and fluid balance disturbed and why are the metabolism, renal function and chemical concentrations altered These disturbances of function can hardly be regarded as adaptive or defensive in character

The theories presented here, and one in Chapter V, illustrate the existing confusion concerning the vascular dynamics of shock An analysis of a few sources for this confusion will be attempted in Chapters IX and X

CHAPTER IX

SIMILARITIES AND DISTINCTIONS BETWEEN SHOCK AND THE EFFECTS OF HEMORRHAGES

CLINICAL similarities between shock and the effects of hemorrhages are so numerous that the results have been regarded as identical and the belief is widely held that hemorrhages will produce the complete syndrome of shock I formerly supported this view as limited to cases in which life is imperiled by hemorrhages "If the reduction of red cells and of blood volume is such that anoxia develops, the minute vessels in extensive areas presently become atonic and the mechanism of shock is superimposed upon the simple circulatory deficiency of hemorrhage This is *hemorrhagic shock* in the true sense It differs from traumatic, toxic or other varieties of shock only in the mechanism by which atony of the minute vessels was produced It does not differ in its gravity nor in its tendency to progress to death "

It was believed that anoxia in the tissues, resulting from the effects of hemorrhages, would cause endothelial permeability, hemoconcentration and other features characteristic of shock Blalock had reported such results, and these coincided with our views at that time, but experiments designed to substantiate that belief produced results which were not anticipated Data concerning these investigations have been published in detail (288[u]), only the results will be summarized here

Repeated efforts were made to demonstrate hemoconcentration during the terminal state when normal unanesthetized dogs were brought to death by repeated withdrawals of small amounts of blood The total amounts withdrawn ranged from 5 6 per cent of the body weight with death in 12 5 hours to 9 1 per cent of the body weight causing death in 31.5 hours. After several withdrawals of blood each amounting to 1 per cent of the body weight, smaller amounts were drawn, when effects became apparent the amounts were reduced progressively to 20 cc and then to 10 cc in order to approach the death point very gradually In no instance was hemoconcentration demonstrable in every case each successive sample of blood was more dilute than the preceding The degree of hemodilution ranged from 50 to 77 per cent in 10 such experiments the average in these was 64 per cent

7

Postmortem examinations were made immediately after death and the visceral appearances in each instance were those characteristic of hemorrhage The tissues were ischemic, pale and dry, there were no engorgement of the minute vessels, no edema nor effusions, and no petechiæ No parenchymal necroses were found by microscopic examination in any of the tissues These visceral findings were substantiated in all the subsequent experiments on hemorrhage (see Figs 5 and 6)



FIG 5 —Photograph of lungs of a dog after death by repeated small hemorrhages All the surfaces and tissues of such lungs are pale, ischemic and dry

In another series the dogs were anesthetized by an intravenous or intraperitoneal injection of amytal, 0 35 gm per kilogram, in order to make continuous records of the arterial blood pressure after hemorrhages The dogs were bled in measured amounts at intervals from the femoral artery or vein The duration of these experiments, from the first bleeding to the death of the animal, ranged from four to thirty-one hours In the experiments of long duration, several bleedings were done on the preceding day with the dogs in a normal state Anesthesia and blood pressure readings were initiated only in the last four to six hours of the experiment The maximal period of anesthesia in this group was 6 5 hours

The results in 13 such experiments differed significantly from those in unanesthetized dogs The loss of smaller volumes of blood caused death and there were variations in the hemodilution which in this group, averaged only 38 per cent In 2 instances after hemorrhages totalling 2 6 per cent and 2 2 per cent of the body weight respectively the blood remained at approximately the same concentration as before bleeding and in 2 instances a slight temporary rise followed by a decline in the concentration

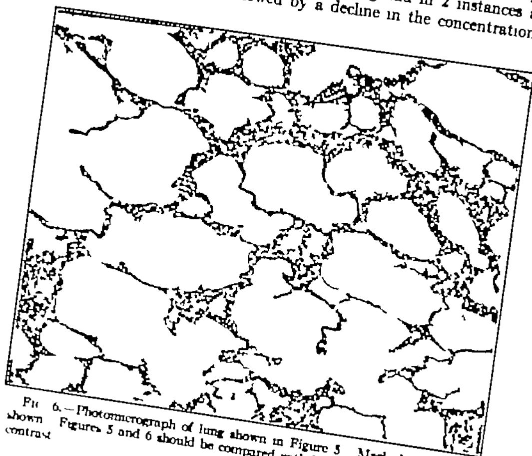


FIG 6.—Photomicrograph of lung shown in Figure 5 Marked ischemia is shown Figures 5 and 6 should be compared with Figures 8 and 9 by way of contrast

occurred These observations are in accord with those of Elman and his associates who reported that the dilution of capillary blood which follows hemorrhage often was absent in dogs under sodium amytal anesthesia and that hemoconcentration some times occurred in the latter These findings suggest that anesthesia may have been a factor in the results reported by Blalock

The volume of blood loss necessary to cause death in four to thirty-one hours in dogs under amytal anesthesia ranged from 2 2 to 6 2 per cent of the body weight averaging 4 0 per cent

The hemorrhages necessary to cause death in unanesthetized dogs in comparable periods of time averaged 7 34 per cent of the body weight This feature is illustrated by a comparison of two such experiments

Dog	*Weight*	*Bled*	*Hours*	*Hemodilution*
346 (No anesthesia)	10 0 kg	9 1% of wt	31 5	77%
373 (Amytal)	10 8 kg	4 48% of wt	31 0	32%

It appears that amytal anesthesia hinders the normal process of hemodilution after hemorrhages and that anesthetized dogs die from the loss of smaller volumes of blood than do normal dogs

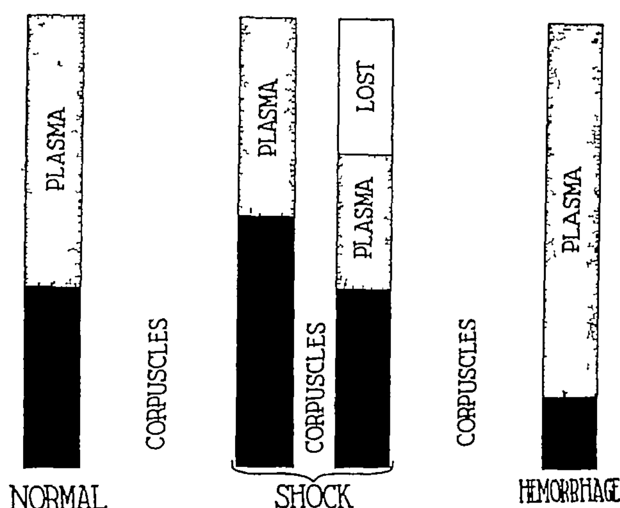


Fig 7 —A volumetric comparison of normal blood with that present in shock and that resulting from hemorrhage

If normal blood (first column) becomes concentrated 40 per cent, it will have the composition shown in the second column Seven cc of such concentrated blood will contain the same volume of corpuscles (third column) as 10 cc of normal blood, 3 cc having been lost In shock with hemoconcentration of 40 per cent, the normal blood has lost 30 per cent of its *total volume* and *50 per cent* of its *plasma volume*

The fourth column illustrates the hemodilution which occurs when the corpuscles have been reduced by hemorrhages to 40 per cent of the normal

Significant differences were noted between the behavior of dogs after hemorrhages and those in a state of shock from the absorption of tissue substance The former were active, did not appear ill, there was neither vomiting, diarrhea, nor evidences of urinary disturbance Dogs in shock uncomplicated by narcosis, are inactive and manifest each of the features of illness mentioned These apparent contrasts led us to make further comparisons, both of observations recorded by others and of features developing

under experimental conditions. Surprisingly few data are on record concerning physiologic disturbances associated with either shock or hemorrhage and no detailed comparison of these has been found

We found that dogs in shock with the blood pressure at a critical level were more seriously affected by the loss of a small amount of blood than were dogs with the blood pressure at the same level

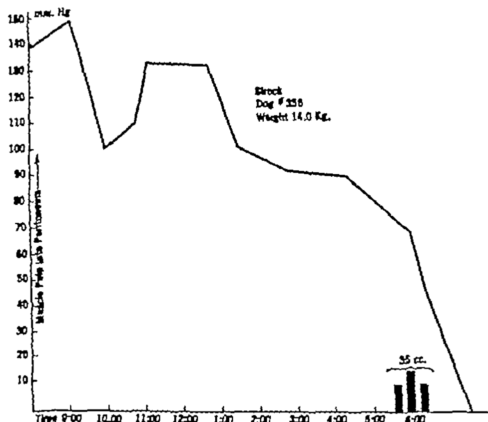


CHART 2 — Blood pressure during shock The scale at the left shows arterial pressure in millimeters of mercury Loss of blood is indicated volumetrically by the height of the shaded columns clock time is shown at the bottom. After the pressure had declined to 72 mm. three successive bleedings totaling 35 cc caused death

from repeated hemorrhages Dogs were anesthetized with amytal, 0 035 gm per kilogram and an arterial canula was connected to a mercuric manometer for continuous record of blood pressure Muscle pulp 4.5 gm per kilogram was then introduced into the peritoneal cavity Later when the mean blood pressure had declined to 70 mm Hg small amounts of blood as 10 to 30 cc, minutes. Other

animals under the same experimental conditions were subjected to hemorrhages only Regularly the dogs in shock succumbed to far smaller hemorrhages than dogs whose blood pressure had been reduced to a critical level by withdrawals of blood This feature is shown graphically in Charts 2 and 3

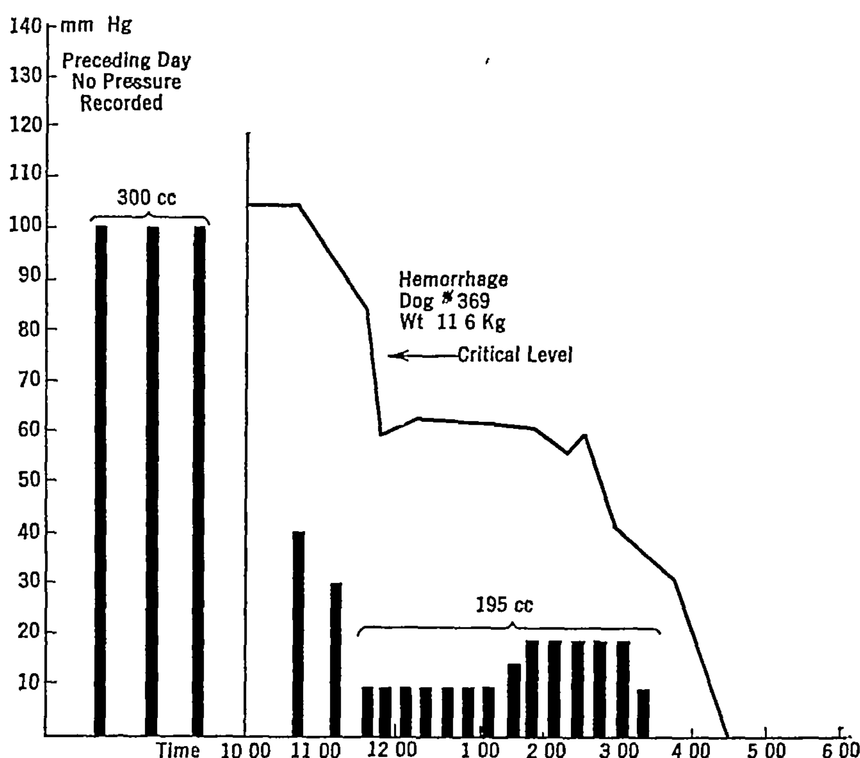


CHART 3 —Blood pressure during hemorrhages Three bleedings, 100 cc of blood each, were done on the preceding day The following day, blood pressure record was instituted under amytal anesthesia The withdrawal of 70 cc of blood brought the blood pressure below 70 mm Hg A further loss of 195 cc of blood, drawn in fourteen successive bleedings, was required to cause death

These results illustrate an observation frequently made that a person or animal in shock may not survive a slight loss of blood which under other conditions would not be serious Also that hemorrhage, when present, is a contributory factor of highest importance

In a previous section (p 15) it was shown that an increased flow of lymph accompanies the effects of various shock-producing agents This is directly related to endothelial permeability and to the resulting disturbances of fluid balance In contrast to this, hemorrhages are followed promptly by a decreased flow of lymph In 2 experiments in which the thoracic duct was cannulated, hemor-

rhages caused a sharp and persistent decrease in the lymph flow This finding is in accord with observations of others upon this effect of hemorrhage (Starling)

The water content of several tissues was determined by weighing accurately the fresh finely minced substance, desiccating it completely and weighing the residue to determine the water loss Care was exercised in taking the specimen from the same area, as of muscle or bowel, in each instance The tissues compared were skeletal muscle bowel wall, pancreas, liver and kidney The water content of these after death by shock in 8 dogs, was compared with that in 8 dogs after death by repeated hemorrhages The water content of the muscle and bowel wall was markedly higher after death by shock, that of the liver was slightly higher and that of pancreas and kidney showed no significant change in this series of determinations. Adolph and his associates reported a marked decrease in the water content of the liver after hemorrhages but found no significant dehydration of skin and muscle

Blalock has reported some unusual observations on visceral changes in shock and after hemorrhages "Edema, visceral congestion and accumulations of fluid in the serous cavities do not occur in shock' (47[1] p 762) Subsequently he stated (47[6,7]) that examination of tissues after death by hemorrhages showed visceral congestion edema and petechial hemorrhages. Later (47[9],) he wrote "The writer has presented proof that *hemoconcentration, an unfavorable response to transfusion and capillary congestion and edema* may be produced in unanesthetized animals by *uncomplicated hemorrhage* (Blalock's italics) The logic of these passages is somewhat eliptical in its course. Some who have been disciplined in the sciences of physiology and pathology may question whether the author gave an objective view of the changes described or whether the pen recorded what the mind pictured.

Physiologists agree in stating that hemorrhage is followed by a transfer of fluid from the tissues to the blood Hemorrhage is 'a most effective way of moving water from outside the blood vessels into the circulating blood' (Adolph) Pathologists regularly have found the tissues to be ischemic and dry when uncomplicated hemorrhages have caused death

Price Hanlon Longmire and Metcalf recently published the first of a series of reports on experimental shock This article recorded observations made in the Department of Surgery, Johns

Hopkins Medical School, on the effects of simple hemorrhages as seen in 37 dogs Their results confirm those which we have described The interval between the first bleeding and the death of the animals ranged between five and six hours Hemodilution occurred regularly, the clotting time was reduced, the plasma chlorides and sodium increased, the potassium and the non-protein nitrogen of the blood rose shortly before death Necropsy showed pallor of the tissues and organs, no edema nor increased wetness of the tissues, no abnormal fluid in serous cavities, no visceral congestion nor evidence of increased capillary permeability was seen They concluded "Evidence is presented to show that capillary atony, 'stasis,' and abnormal permeability of capillaries probably do not occur in dogs following uncomplicated acute hemorrhage "

A serious derangement of fluid balance is an outstanding feature of shock It is evidenced by the hemoconcentration, the increased flow of lymph, the reduced blood volume, the increased water content of the tissues, by the inability to absorb fluid from the gastro-intestinal tract or from the tissues, and by inability to retain fluid introduced directly into the blood

Patients or animals affected by simple hemorrhages will absorb fluids from the tissues, thus restoring the blood volume Suitable fluid given intravenously will be retained because endothelial permeability has not been increased and the mechanism of fluid balance is not notably impaired

Delayed coagulability of the blood as a characteristic feature of shock was discussed in Chapter II We found the clotting time markedly lengthened in 10 dogs in shock After hemorrhages the formation of fibrin is accelerated and the clotting time is shortened (Best and Taylor) This acceleration is detectable within ten minutes after the hemorrhage (Castle and Minot) In our experiments, the blood of dogs clotted normally in eight to twelve minutes After each successive bleeding the coagulation was more rapid and, when the blood pressure had declined to the critical level, the blood clotted completely in one to four minutes A marked increase in the speed of coagulation occurred after hemorrhages in 9 out of 10 animals on which observations were made In 1 animal no significant change occurred

We undertook a comparison of the chemical and other hematologic changes which occur during shock and after hemorrhages It was realized that data derived from moribund animals are not so reliable and may show variations not present before the animals

were in a dying condition In order to obviate this source of error, blood was drawn for examination when hemoconcentration or hemodilution indicated that the circulation was seriously affected by shock or by hemorrhage, respectively When continuous record of blood pressure was made, blood for chemical tests was drawn when the pressure had declined to a critical level of 70 mm Hg In 4 dogs shock was induced by autolysis of muscle pulp in the peritoneal cavity in 2 dogs by repeated subcutaneous injections of histamine and in 2 by anaphylaxis (horse serum)

Hemoconcentration, as shown by erythrocytic counts hemoglobin and specific gravity readings occurred regularly during shock and hemodilution resulted without exception after bleedings

There was a marked increase in the non-protein nitrogen during shock in each instance, a moderate decrease was found in 4 out of 6 dogs after hemorrhages. In 2 there was a slight increase

The chloride content of the plasma declined moderately in 5 out of 7 dogs during shock in 2 there was no significant change The chlorides increased in 5 out of 6 dogs as a result of bleedings

There was a marked decline in the CO_2 content of the plasma both in shock and after hemorrhages. The blood sugar varied irregularly during shock but a marked increase occurred regularly after hemorrhages Hence neither blood sugar nor reserve alkalinity are points of distinction between these conditions.

Discussion.—Several workers (Blalock, Freeman and their associates) reduced the blood pressure of dogs below 70 mm Hg by the repeated withdrawal of blood from the femoral artery When the arterial pressure sank blood was introduced by direct transfusion when it rose above 70 mm a quantity of blood was again removed By this combination of removal and reintroduction of blood the pressure was maintained at about 70 mm Hg for several hours. The animals showed a number of the clinical features of shock weakness pallor thready pulse and low blood pressure Hemoconcentration was found in all such experiments. 'Particularly impressive is the finding that *all animals died despite the fact that more blood was introduced than had been removed* ' In other words transfusion was without benefit after low blood pressure had existed for an extended period *Examination of the tissues after death showed visceral congestion edema and petechial hemorrhages* (italics by Moon) It was concluded ' these observations prove that shock can be produced by uncomplicated hemorrhage and that hemoconcentration a negative response to trans-

fusion and alterations in the tissues result if the circulation remains depressed for several hours "

Before accepting these deductions *in toto*, the conditions of the experiments should be examined thoughtfully Starling showed that arterial pressure below 80 mm Hg is insufficient to nourish the myocardium, hence when the pressure remains below that level for a time, circulatory failure of cardiac origin supervenes It is known that neither man nor animals can long survive if arterial pressure is maintained, by whatsoever means, below the level mentioned This was exemplified in the experiments of Cannon and Cattell in which a device for producing adjustable hydrostatic pressure was applied on the outside of the heart This limited its filling, also its volume output, and reduced the arterial pressure correspondingly After the blood pressure had been held below 80 mm for a time, the device was removed but the circulatory efficiency was not restored and the animals died

Certainly, when the blood pressure is maintained at 70 mm continuously by hemorrhage or by any other means, a point will be reached after which neither transfusion nor any other procedure will restore circulatory efficiency Animals so treated inevitably will die In the experiments first cited, an item was overlooked which bears directly on the validity of the conclusions When an animal is dying *from any cause* there is relaxation of vascular tonus affecting particularly the capillaries and venules Anoxia which regularly accompanies the moribund state, causes abnormal permeability of endothelium If now a quantity of blood is introduced, it will distend the atonic vessels and will produce visceral congestion If death does not occur immediately, leakage of plasma will cause both edema and hemoconcentration In the experiments mentioned, *more blood was reintroduced than had been withdrawn,* this would accentuate the effects mentioned The same effects would be expected to follow if animals moribund from any cause whatsoever, were given copious transfusions of blood

Some may interpret such results as demonstrating that vascular atony and endothelial permeability occur whenever an animal is moribund If these atonic vessels are distended by copious transfusions, the resulting congestive phenomena described by the authors would resemble those which are characteristic of shock It seems that these appearances of the viscera were in a sense artificially produced, they did not result from simple hemorrhages, and that their significance was unduly magnified by the authors

We have been unable to demonstrate hemoconcentration and

the visceral pathologic changes of shock in animals brought to death by repeated losses of blood Nevertheless we believe that capillary atony and endothelial permeability develop as terminal events when an animal is moribund from hemorrhages or from any other cause. A highly important difference between shock and the effects of hemorrhages, as we see it, is that endothelial injury and the resulting disturbances of circulation and of fluid balance occur as initial derangements causing shock, while those same disturbances develop only in the terminal or moribund state after hemorrhages

Summary —Several features in the syndrome of shock occur also after hemorrhages because either evokes the same physiologic mechanism for counteracting the disturbances. These points of resemblance are arranged below in outline form

Items Identical in Both Conditions

- Sympatho-adrenal activity
  - Stimulation of myocardium
    - *Strong rapid pulse in early stages
  - *Peripheral vaso-constriction
    - Reduced volume flow
    - *Peripheral ischemia pallor
    - *Loss of tissue turgor
  - Discharge of reservoir blood into systemic circulation
    - *Contraction of spleen
  - *Increased blood sugar
  - *Dilatation of pupils, often perspiration
- Low basal metabolism
  - *Declining temperature
- *Decreased alkaline reserve
- *Decreased serum protein
- *Increased respiratory rate, thirst
- *Low arterial blood pressure (in late stages)
- Death due to inadequate circulatory function

Incipient circulatory deficiency from shock, hemorrhage or other causes evokes compensatory reactions by the sympatho-adrenal system resulting in identical responses Most of the definitions which have been proposed for *shock* are combinations of the above items, hence no distinctions from the effects of hemorrhage were evident and the two conditions were regarded as identical

We have assembled the various physiologic and biochemical

* We have verified experimentally the findings in the items marked with an asterisk.

features which have been reported in shock from wounds, burns, intestinal obstruction, anaphylaxis and other causes, also reports on the same items as observed after uncomplicated hemorrhages These have been arranged in tabular form to facilitate comparison

Items	*Shock*	*Hemorrhage*
*Endothelium	Permeable to colloids	Impermeable to colloids
*Flow of lymph	Increased	Decreased
*Tissue fluid	Increased	Decreased
*Fluid balance	Disturbed	Undisturbed
*Pulmonary edema	Frequent	Absent
*Absorption, gastro-intestinal	Impaired	Unimpaired
*Absorption from tissues	Impaired	Unimpaired
*Vomiting	Persistent	No vomiting
*Diarrhea	Frequent	Absent
*Effect of moderate loss of blood	Severe	Mild
Transfusion of blood	Ineffective	Effective
*Saline solutions, intravenous	Ineffective	Often effective
Renal		
*Excretion	Deficient	Unimpaired
*Urine	Concentrated, low volume, albumin, erythrocytes, bile, débris, etc	No characteristic changes
Blood		
*Coagulation time	Lengthened	Shortened
*Hemoglobin, erythrocytes	Increased	Decreased
*Specific gravity	Increased	Decreased
*Non-protein nitrogen	Increased	Decreased
Potassium	Increased	Terminal increase
Magnesium	Increased	Decreased
*Plasma chlorides	Decreased	Increased
Necropsy Findings		
*Edema of soft tissues	Characteristic	None
*Serous effusions	Present	Absent
*Capillo-venous congestion	Characteristic	Absent
*Petechiæ	Characteristic	Absent
*Visceral ischemia	Absent	Present
Organ weight	Increased	Decreased
*Gastro-intestinal tract	Dilated, atonic	Contracted
*Parenchymal necroses	Present	Absent

Medical history records instances in which a symptom complex, once regarded as a disease entity, later was shown to comprise

* We have verified experimentally the items marked with an asterisk

several more or less unrelated conditions. The terms *leprosy* and *Hodgkin's disease* originally were applied to groups of conditions having clinical resemblances but later shown not to be identical Few terms have been used more loosely and indefinitely than *shock* Hence it is not strange that the effects of hemorrhage, which clinically resemble shock so closely, should have been included without discrimination in the broad application of that term

It is remarkable that numerous important differences so long have escaped the attention of those interested in these conditions We humbly admit our own error in subscribing at one time to the belief that uncomplicated hemorrhages will produce the syndrome of shock

Conclusions —Points of similarity between shock and the effects of hemorrhages result in part from the fact that each evokes the same mechanism of compensation and in part from the deficiency of circulation which each produces

Points of contrast between shock and the effects of hemorrhage are so numerous that the assumed identity of those conditions is no longer tenable

Hemorrhage, when present, is a highly important contributory factor because the derangement of fluid balance which accompanies shock, interrupts the processes by which loss of blood is com pensated

For the sake of accuracy, the expression *shock and hemorrhage* should be substituted for the term *hemorrhagic shock*

We urge that investigators should not employ hemorrhage as a means for producing shock experimentally If the results so obtained are interpreted as applying to shock erroneous con clusions may be drawn

CHAPTER X

SOURCES OF CONFUSION

It was suggested in the *Foreword* that four chief causes have operated to delay final clarification of the mechanism of shock. The first of these, *inadequate knowledge of endothelial function and of capillary reactions*, has been obviated by investigations on the physiology and pathology of capillaries. The second major hindrance was *a belief in the identity of shock and the effects of hemorrhage*. This will no longer cause confusion if the relationship between these conditions, as set forth in the preceding chapter, is comprehended. A third confusing factor consists of *sources of error in experimental methods and in deductions*. It is appropriate here to explore the latter and to consider why intensive investigations, by diligent and conscientious workers, have led to divergent conclusions.

Effects of Anesthesia.—One of the major factors contributing to circulatory failure from operations and injuries, is the effect of deep anesthesia. As early as 1876, Blum had noted this effect and had advised against general anesthesia with chloroform when operating on men suffering severe wounds. Military surgeons have reported that frequently a wounded soldier, whose apparent condition was not critical, developed profound shock immediately when anesthetized for operation. Such occurrences are not rare in the experience of surgeons who have to deal with severe accidental injuries.

Dale found that histamine, 1.0 to 2.0 mg. per kilogram, caused immediate fatal shock when given by injection to cats under ether anesthesia. Unanesthetized cats showed only transient effects when given 10 times that dosage of histamine. Mann concluded that in many experiments the workers were dealing chiefly with the effects of the anesthetic rather than of shock, and that this accounts for much of the confusion concerning the latter.

My associates and I began our studies on shock by the methods commonly used for such experiments. Very early in these studies, a healthy normal dog was given sodium phenobarbital, 0.3 gm. per kilogram, and an arterial cannula was inserted preliminary to inducing shock by trauma. Shortly the blood pressure declined progressively a total of 93 mm. Hg although no experimentation

had begun We immediately abandoned barbital as an anesthetic, and acquired a distrust for data derived from such experiments Robinson and Parsons recorded the observation that some of their dogs under barbital anesthesia, developed "spontaneous shock ' Blalock recorded similar experiences and attributed the decline in blood pressure to "abnormal sensitivity to barbital" He wrote ' In several animals there was a rapid decline in the blood pressure shortly *after giving the barbital* These experiments were discarded The level of the mean blood pressure was used as a criterion of the degree of shock " One infers that when experimentation had begun before the pressure fell the results of such experiments were considered dependable Apparently a *control on this factor of the experiment was not regarded as* essential It was recorded that in one instance a dog under barbital anesthesia succumbed to a loss of blood amounting to only 1 5 per cent of his body weight. In 2 other dogs in the same series, death occurred from the effects of barbital without any loss of blood Yet such abnormal susceptibility to injury or hemorrhage under barbital anesthesia has not been considered as a possible factor of error by authors who used this method

Gruber and Baskett studied the circulatory effects of sodium barbital and of sodium phenobarbital Moderate doses of these (05 to 0 5 gm) caused the blood pressure to decline in 162 out of 164 animals on which such tests were made Morgan and I produced sublethal shock in dogs, as shown by hemoconcentration and by the visceral changes seen postmortem, by causing deep narcosis with sodium phenobarbital given by mouth A recent treatise on Pharmacology states "Large doses of barbital depress the central vasomotor center and peripheral vasodilatation and hypotension follow Barbiturates also can produce dilatation of the finer blood vessels by *a direct effect on their musculature*, and may dilate and injure capillary beds to such an extent that shock ensues (Goodman and Gilman)

It seems remarkable that investigators have failed to consider the effects of deep narcosis upon the blood pressure When variations in pressure are used as a criterion for shock, the magnitude of this factor of error is incalculable

Factors in Traumatic Shock.—It was recognized that shock, occurring under conditions of warfare often resulted from a combination of factors rather than from a single one These included absorption from injured areas, delay in operative treatment, anesthesia hemorrhage and others Shock following accidental

injuries includes combinations of the same factors The circulatory failure which develops after surgical operations combines the effects of the disease which necessitated the operation, the anesthetic, the trauma to various tissues, and such hemorrhage and loss of fluid as resulted from the operation itself Although the surgeon may assume, in a given case, that one or another of these is the chief factor, it usually is not possible to secure definite evidence supporting the assumption nor to evaluate accurately the importance of the other factors

Most of the methods used for producing shock experimentally likewise entailed combinations of similar contributory factors Highly important among these is anesthesia, as discussed in the preceding section Hemorrhage and loss of fluid into injured or inflamed tissues is another complicating factor of high importance It is known by everyone that extensive hemorrhage will cause a decline in blood pressure and other signs of shock In many of the experiments reported, the hemodilution which occurred before death, the extensive hemorrhages found in the traumatized areas and the pale, ischemic appearance of the viscera after death—all supported the authors' contention that hemorrhage was the predominant factor in those experiments However, those experiments provided no means for evaluating the effects of absorption nor of anesthesia

A Combination of Factors.—The circulatory deficiency which develops after wounds and operations is the summative effect of several factors Most of the experimental work on shock was based upon combinations of the same factors For purpose of illustration, the three most important of those items may be designated as follows

Let X symbolize the effects of hemorrhage and loss of fluid
Let Y symbolize the effects of anesthesia
Let Z symbolize the effects of absorption from damaged tissues

Then shock resulting from trauma, burns or surgery, and that produced experimentally by tissue abuse, may be represented by the formula

$$X+Y+Z = SHOCK$$

A single equation containing two or more unknown quantities is as undependable in medical science as in mathematics Experiments in which these items are combined merely prove that the sum total of the effects caused circulatory failure of the type called shock Such experiments can have absolutely no value as indicating the relative importance of the individual items It is

absurd even to assume that those items will have the same relative value in any two cases or experiments, for their values in such a combination are essentially those of indeterminate variables

The method commonly used in studies on shock is to narcotize an animal deeply with barbital or a similar drug An arterial cannula is inserted, and the blood pressure and pulse rate are recorded kymographically through a manometer Variations in these have been used as the sole criterion of shock in most of the experimental work reported Shock is then induced by extensive trauma to the muscles by prolonged manipulation of the intestines or by some other form of tissue abuse Such methods are open to serious objections

A decline in blood pressure is not an accurate criterion It often results from other conditions and it does not occur early in shock but appears only after both blood volume and volume flow have been reduced

The deep narcosis used often causes low blood pressure and other shock like manifestations

Variable amounts of blood and fluid are lost incident to trauma In some reports the workers showed convincing evidence that they were dealing almost entirely with hemorrhage

Under such conditions of experimentation the recorded phenomena may be due either to the narcotic, or to absorption, or to the associated hemorrhage, or in part to each Yet, ignoring the effects of absorption and of anesthesia, far reaching conclusions were drawn as to the origin of the condition under consideration

It may be stated with assurance that *the combination of indeterminate variables described is responsible for much of the confusion which has surrounded the problem of shock* This statement does not imply criticism of any author or group it merely directs attention to uncontrolled factors in the experimental method formerly used

A REVISION OF METHODS

Dependable studies on the possible effects of absorption must not have the character of an equation containing several unknown quantities In making such studies the chief problem is to eliminate anesthesia and hemorrhage as confusing factors. When kymographic records of blood pressure are used as the criterion for shock it is necessary that the animal be deeply anesthetized To eliminate the effects of hemorrhage and of anesthesia, a new method of experimentation was evolved

Hemoconcentration (see Fig 7) had been shown to be an early and regular feature in shock resulting from wounds, it also had been employed as a test useful in differentiating shock from hemorrhage and in estimating the clinical condition of wounded men Preliminary trials of this test gave satisfactory and gratifying results It was found that hemoconcentration occurred long before the arterial pressure declined, both in clinical cases and in experimental shock Accordingly hemoconcentration, in place of blood pressure, was used as a diagnostic criterion in a series of experiments

The next problem was to arrange for the absorption of cytoplasmic substances without the confusing effects of either hemorrhage or anesthesia One method for accomplishing this was as follows

A normal dog was anesthetized and killed The skin over the thigh was shaved, scrubbed with soap and sterilized with Harrington's solution followed by alcohol A quantity of muscle was then excised, ground finely in a meat chopper and suspended in saline solution Sterile instruments were used and rigid precautions against contamination were observed.

A normal dog was then anesthetized lightly with ether while a slit about 1 inch long was made in the abdominal wall A quantity of muscle pulp suspended in saline solution, was introduced into the peritoneal cavity through a funnel The incision was then closed with sutures Records were made of the pulse rate, temperature, and of the hemoglobin and red cell count before the operation and at intervals of two or three hours afterward

This procedure provided conditions under which the uncomplicated effects of absorption could be studied No blood was lost by the operation, and the effects of the ether were regarded as negligible The anesthesia lasted only approximately ten minutes The dogs recovered promptly and were normally active for several hours until the effects of absorption developed

Severe illness developed within two or three hours when large doses, 4 gm to 5 gm per kilogram, were used Thirst was evident but drinking was followed by vomiting The vomitus contained bile, mucus and flecks of blood The urine was scanty and often was tinged with blood Diarrhea frequently developed and the feces contained mucus and traces of blood The pulse rate and temperature rose and, although the peripheral parts became cold, the rectal temperature remained high until death The peripheral circulation was almost abolished and it was difficult to obtain

blood by venipuncture because of the emptiness of the veins. Also it was sometimes difficult to obtain capillary blood from ears nose or paws for determining hemoconcentration This developed regularly, sometimes beginning within an hour after the implantation of muscle pulp The concentration increased progressively and its degree was proportionate to the apparent illness of the animal A condition of collapse, relaxation and stupor preceded death

Smaller doses of muscle pulp produced the same signs of illness but it was slower in development and less marked in degree Death did not occur so early recovery often resulted when doses less than 2.5 gm. per kilogram were used The accompanying tabulation records the progress of one of our earliest experiments on the effects of absorption

TABLE 1 —CONCENTRATION OF BLOOD AS SHOCK DEVELOPS

Hour	*Specific gravity*	*Hemoglobin percentage*	*Red cells*
6.30 A.M	1 060	101	5 110 000
7:00 A.M	Muscle substance into peritoneum		
10.30 A.M.	1 065	94	4,860 000
1.30 P.M	1 065	104	5 694 000
3.20 P.M	1 067	108	5 696,000
4.50 P.M	1 075	120	6,400 000
5 15 P M	1 075	130+	7 450,000

Exactly the same type of results followed similar implantation of the substance of liver kidney and brain When watery extracts or autolysates of tissues were injected intravenously or intra peritoneally illness and hemoconcentration developed immedi ately These produced effects of the same kind as followed similar injections of histamine This type of experiment was made on more than 200 animals and the results were uniformly of the same character The animals included dogs, cats, rabbits monkeys and guinea pigs.

The formula, X+Y+Z = Shock, was simplified by eliminating items X and Y The results of this new method of experimentation indicate that circulatory failure of the shock type may result from absorption independent of hemorrhage, of local loss of fluid and of anesthesia The absorption of normal tissue substance, or of products derived from autolysis of tissues, appears to be the important etiologic factor under the conditions of these experi ments.

Autolysis in Vivo —The results of Mason, Andrews and others

(see Chapter VII), who produced shock by the autolysis of liver tissue *in vivo*, have been interpreted by some as due to peritonitis caused by bacterial growth in the liver substance and in the peritoneal fluid Ellis and Dragstedt suggested this explanation and reported experimental results in support of it By Caesarean section on a pregnant bitch near term, they removed pups aseptically and placed the whole fetal livers in the peritoneal cavities of normal healthy dogs, in some experiments they implanted the entire abdominal viscera No toxic effects resulted from these procedures and they concluded that the results in the experiments of Mason and associates probably were due to infection

Subsequently Andrews and Hrdina repeated with aseptic material, the previous experiments on autolysis Fresh dog liver was autolyzed for twenty-four hours, then autoclaved and its sterility was proved by cultures This substance, in a dosage of 100 gm each, was placed in the peritoneal cavities of four normal dogs, each dog died within sixteen hours In other experiments *fresh* dog liver was autoclaved, proved sterile by culture and implanted intraperitoneally as before This produced the same result as autolysed liver in 4 out of 6 dogs so treated They concluded that the reactions described were not due to infections since they could be produced by sterile material Their chemical studies on the liver autolysate indicated that the toxic agent is water soluble and thermostabile Results of precipitation and Biuret tests indicated that the substance belongs in the albumose group

Since similar objections have been raised regarding our autolysis *in vivo* experiments with muscle, liver, kidney and other tissues, a more detailed consideration of the conditions and results is in order

Intracellular enzymes are destroyed by heat, hence autoclaved tissues will *not* autolyze but gradual proteolysis will result from the action of enzymes and leukocytes present in the peritoneal fluid Obviously, the products of protein digestion will be formed and absorbed more slowly under this condition, and the effects on the animals will be less rapid and less severe We have verified this fact experimentally, Kennedy and I found that when autoclaved muscle pulp was implanted, shock was delayed and less severe than when fresh muscle pulp was used

Absorption is greatly retarded if tissue is implanted *en masse* as compared with finely ground or pulped tissue This is illustrated in the results of experiments by Parsons and Phemister The

rectus abdominalis muscle was excised aseptically and reimplanted intraperitoneally in 2 dogs and into its bed in 1. The animals showed no signs of intoxication during a subsequent period of three weeks. Assuming that the mass of muscle used amounted to 40 or 50 gms. it can be stated with assurance that shock would have resulted if the muscle substance had been finely ground. It would be of interest to repeat the experiment of Ellis and Dragstedt using sterile *pulped* fetal tissue rather than whole organs.

We found that the effects of absorption depend in part upon the distribution of the pulped tissue. In one of our early experiments, muscle pulp 4 gm per kilogram was implanted as described, the dog became ill as shown by vomiting, loss of appetite, hemoconcentration and other signs but gradually recovered. When this dog later was killed and examined, the entire mass of pulp was found wrapped in omentum, softened and compacted together and partly encapsulated by proliferative fibrosis. We believed that absorption had been so retarded by the omental wrapping and by the localizing effect of the inflammatory reaction to the foreign substance, that the usual fatal effects had not developed. In all subsequent experiments of this type, we have used particular care to distribute the pulped tissue among the viscera of the abdominal cavity. Under this condition a dosage of 3 gm per kilogram of pulped tissue has produced fatal shock almost without exception.

The peritoneal membranes respond to tissue pulp with an inflammatory reaction like that induced by cytoplasmic substance in contact with living tissues in general.[1] Congestion, transudation of fluid and emigration of leukocytes takes place but the diffuse capillary congestion and edema found in other visceral areas as the lungs, liver and kidneys (see p. 130) indicated that the endothelial effects were general and were not limited to the peritoneum. The fluid lost into the peritoneal cavity is not sufficient to disturb the systemic circulation. In many instances *no fluid is lost* as we determined by actual measurement. Since the data on this feature have not been published details will be given here. Weighed amounts of muscle pulp suspended in measured volumes of normal saline solution were introduced into the peritoneal cavities of normal dogs in order to obtain data on the resulting biochemical alterations (see Chapter IX). Autopsy

[1] For a discussion of cytoplasmic substances as related to inflammation and shock see *Shock and Related Capillary Phenomena*, Chapters IV, V and IX.

was performed immediately after death and the residue of fluid and pulp was collected from the peritoneal cavity with scrupulous care A tared sponge was used to collect fluid from all parts of the abdominal cavity, the sponge was weighed with the fluid and pulp, and the tare was subtracted This was done in a group of 10 consecutive experiments on shock by autolysis The results are tabulated below

TABLE 2 —VOLUME OF FLUID LOST BY ANIMALS IN SHOCK

Dog No	*Weight kg*	*Pulp and saline introduced*		*Pulp and fluid recovered gm*	*Difference gm*
355	12 0	50 gm	100 cc saline	239	+89
356	14 0	63 "	100 "	160	− 3
357	12 0	54 "	100 "	154	0
359	10 5	48 "	100 "	112	−36
361	10 8	49 "	100 "	110	−39
362	9 1	41 "	100 "	90	−51
363	8 6	25 "	50 "	95	+20
370	13 0	43 "	100 "	300	+57
376	8 0	24 "	100 "	100	−24
384	6 7	20 "	100 "	128	+ 8

It is seen that in half of these experiments the amount of fluid in the peritoneal cavity at death was actually less than that introduced In 4 instances there was an increase ranging from 8 to 89 gm The loss of 89 cc of fluid during 10 5 hours by a dog weighing 12 kg would not appear to be a major factor in causing death Amounts of plasma larger than this may be removed at one time by plasmapheresis without producing notable effects

The fluid present in the peritoneal cavity after death in such experiments is pinkish and turbid because of tissue fragments and débris suspended in it Varying numbers of leukocytes are found but not in sufficient numbers to give it the characteristic of an inflammatory exudate A type of large Gram-positive bacilli is usually present in the fluid described These are saprophytes of the kind which can be cultivated from the liver, kidney, muscle or brain substance of normal dogs We have injected massive cultures of these intraperitoneally in normal dogs without apparent effect Quantities of the turbid fluid mentioned may be transferred to the peritoneal cavity of another dog, equally without effect It is recognized that the growth of bacteria may hasten the proteolysis of the implanted tissue, but similar bacterial action would be a factor in the devitalized tissues about battle wounds

and accidental injuries, for all such wounds are grossly contaminated

For several additional reasons, the cause for death in such experiments obviously is not infection Andrews and Hrdina state that complete transection of the bowel, allowing the discharge of fecal material into the peritoneal cavity will not cause death in so short a time as the intraperitoneal autolysis of liver substance This statement is corroborated by the fact that in our experiments shock often has ended fatally in six to ten hours from autolysis of muscle substance in the peritoneum We know of no form of infection which can be induced in dogs with such results. Let it be remembered that dogs are highly resistant to peritonitis and that it can be induced in them only with great difficulty

The signs of illness which accompany tissue autolysis *in vivo* are not like those of infection but are indistinguishable from those of shock from severe burns, histamine poisoning anaphylaxis or the intravenous injection of venoms, proteoses, bile, bile salts and the like The disturbances of renal function and the blood chemical changes are of the same nature during experiments by autolysis and in each of the conditions mentioned, also these changes are of the same pattern in traumatic shock in man (for items see Chapters II and IX)

It is well known that damaged or necrotic tissues undergo autolysis which releases intermediate products of protein cleavage Numerous experiments have been cited in which watery extracts of normal tissues, autolysates and proteoses have caused circulatory disturbances of the shock type when introduced into normal animals The results from autolysis *in vivo* indicate that similar effects may follow when the *animals own tissues are injured*

Let it be noted that autolysis *in vivo* is *only one* of a wide variety of means by which we have produced shock experimentally Emphasis on its significance has been necessary because many have not been convinced that the absorption of products from damaged tissues is a factor in causing shock after extensive trauma

Summary —Much of the confusion concerning the mechanism by which shock develops, has arisen because of uncontrolled factors in the experiments. When anesthesia, hemorrhage and absorption of substances from traumatized tissues are combined in the same experiment it is impossible to determine which factor caused the circulation to fail the recorded results may have been

was performed immediately after death and the residue of fluid and pulp was collected from the peritoneal cavity with scrupulous care A tared sponge was used to collect fluid from all parts of the abdominal cavity, the sponge was weighed with the fluid and pulp, and the tare was subtracted This was done in a group of 10 consecutive experiments on shock by autolysis The results are tabulated below

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Let it be noted that autolysis *in vivo* is *only one* of a wide variety of means by which we have produced shock experimentally Emphasis on its significance has been necessary because many have not been convinced that the absorption of products from damaged tissues is a factor in causing shock after extensive trauma

Summary —Much of the confusion concerning the mechanism by which shock develops, has arisen because of uncontrolled factors in the experiments. When anesthesia, hemorrhage and absorption of substances from traumatized tissues are combined in the same experiment, it is impossible to determine which factor caused the circulation to fail, the recorded results may have been

due to the anesthesia, to the local loss of blood and fluid, to absorption, or in part to each of these

Experiments were so arranged as to eliminate narcosis, trauma and the accompanying hemorrhage and local loss of fluid Under these conditions it has been shown repeatedly that autolysis of normal tissues *in vivo* will produce the complete syndrome of shock

The results of these experiments on absorption coincide with observations on the effects of tissue extracts and products of protein cleavage cited in Chapter VII They corroborate the theory of *traumatic toxemia* by relating it directly with capillary pathology That relationship is verified by the methods of pathology in the subsequent chapter

CHAPTER XI

THE PATHOLOGY OF SHOCK

A REVIEW of medical literature reveals the remarkable fact that no pathologist has undertaken a study of shock, nor have the methods of pathology been applied by others in their investigations. Apparently the belief that shock is purely a physiologic disturbance, unaccompanied by significant morphologic changes, had been accepted without question.

Yet there are numerous instances in which the appearances of the viscera were recorded *without comment on their significance*. When seen in the light of present knowledge concerning capillary pathology, these changes described in the viscera were visible evidence of endothelial damage. Curnin (1823) described edema, effusions and the deeply congested appearance of the viscera, the serosæ and mucosæ, after death from burns. These changes have been confirmed as the characteristic visceral alterations resulting from extensive burns of the skin (see Chapter XII).

Dale and associates recorded the appearance of the organs of cats after histamine shock. The viscera had a dull dusky red color and the minute vessels were visibly distended and tortuous. Rich gave histamine to animals both by local application and by injection, and recorded its visible effects both *in vivo* and *post mortem*. Congestion, dilatation, stasis and permeability of capillaries were found. These confirmed the interpretations of Dale and others that shock from histamine is due to its effects on the walls of the minute vessels.

Turck noted cyanotic congestion of the viscera after shock produced by injecting extract of tissues. Whipple and associates produced shock in dogs by injecting fluid obtained from obstructed loops of bowel, also by injecting extracts of intestinal mucosa. They reported marked congestion of the lungs, liver, kidneys and of the abdominal viscera. Microscopic examination showed engorgement of the minute vessels and evidence of circulatory stasis in the areas mentioned.

Sherrington and Copeman (1893) recorded the development of edema in the tissues, incident to experimental shock. Bayliss described vascular engorgement in the intestines of cats after shock produced by trauma and by the injection of extracts of

muscle Cornioley and Kotzareff described the hemorrhagic and hyperemic appearance of the lungs, gastro-intestinal tract, liver and other viscera after traumatic shock in rabbits and guinea pigs

Keith described marked pulmonary congestion and edema after fatal shock from battle wounds He stated that other tissues were abnormally moist Congestion and edema of the internal organs are given as pathologic findings after wound shock, in the History of the Medical Department of the United States Army in the first world war.

Erlanger and associates recorded the appearance of the viscera after shock produced in several ways Congestion of various tissues was the most prominent feature The intestinal mucosa, especially of the ileum, had the appearance of purple velvet and contained numerous punctate hemorrhages The large venous channels were collapsed and relatively bloodless but the venules and capillaries were engorged "The most remarkable feature though is brought to light by microscopic examination of the intestines in all types of shock the capillaries and venules of the villi are tremendously distended by solid masses of red corpuscles " They stated that the findings were uniform in more than 100 dogs used in such experiments

These authors are among the few who sensed a significant relationship between the visceral changes described and the mechanism of the circulatory deficiency They found hemoconcentration and decreased blood volume as regular features during shock They attributed these to the leakage of plasma into the tissues This, and the sequestration of blood in the dilated capillaries and venules, reduced the blood volume and impaired the circulatory efficiency

Morphologic Changes in Experimental Shock.—The observations cited led us to undertake experiments on shock for the purpose of making gross and microscopic studies *post mortem* It was hoped that these might supply evidence contributing toward an understanding of the origin, nature and mechanism of that condition The method described in the preceding chapter was devised for producing shock by absorption, uncomplicated by trauma, hemorrhage and anesthesia Thirty dogs were used in the first series of experiments by this method The following is representative of the results in this series

A healthy female mongrel dog, weighing 9 0 kg, was given 36 gm of muscle pulp in 200 cc of sterile saline solution intraperitoneally at 2 00 P M Illness with vomiting and diarrhea

began a few hours later The urine was scanty and brownish in color On the next day the dog refused food but drank copiously, this was followed each time by vomiting The dog was inactive, irresponsive when disturbed and evidently was very ill The red cell count rose from 6,350,000 before the experiment to 7,600 000 at 10·00 A M. and to 9,000 000 at 6 30 P.M. on the following day These counts represent concentration of 16 per cent and of 40 per cent respectively, the tissues of the limbs lost their turgor and became flabby, the peripheral veins were collapsed and empty and the ears, nose and paws were cold to the touch Death occurred about thirty hours after the implantation

Postmortem examination revealed intense congestion of the peritoneal and pleural surfaces The venules in the omentum were distended and those along the mesenteric attachment were abnormally prominent, engorged and tortuous. The mucosa of the gastro-intestinal tract had a deep purplish cyanotic color, and the lumen of the tract contained bloody mucus. The lungs were deeply congested (see Fig 8), likewise the liver and kidneys Blood oozed and dripped from the parenchyma of the liver The spleen was contracted, firm and relatively bloodless. There was moderate hyperemia of the adrenals, pancreas, pericardium and meninges, also of the conjunctivæ. The peripheral parts of the body were pale and ischemic

On microscopic examination the tissues of the viscera in general showed marked distention of the capillaries and venules. Those in the aveolar septa of the lungs were abnormally engorged (Fig 9) The small vessels in the intestinal villi were distended with closely packed corpuscles and there were numerous capillary hemorrhages in the lungs, mucosæ, and kidneys (Fig 10) The splenic pulp was not congested but contained very few red blood cells. Acute parenchymatous degeneration was seen in the myocardium liver and kidneys.

These findings corroborate the observations of the authors referred to in the early part of this chapter The most significant features were the evidence of capillary damage in most of the viscera. The closely packed corpuscles in their lumina indicated circulatory stasis and the microscopic hemorrhages showed not only capillary atony but dissolution of the endothelium

Exactly similar signs of illness developed in each of the other animals in that series The accompanying hemoconcentration ranged between 20 and 50 per cent In many instances the vomitus, feces and urine contained visible traces of blood Four

dogs, which had received muscle pulp in doses of 3 gm per kilogram or less, recovered The signs of illness were less marked in these, and in no instance did the hemoconcentration rise above 20 per cent This subsided as the animals recovered Death occurred in from ten to sixty hours in 23 of the dogs and in four to six days in 3

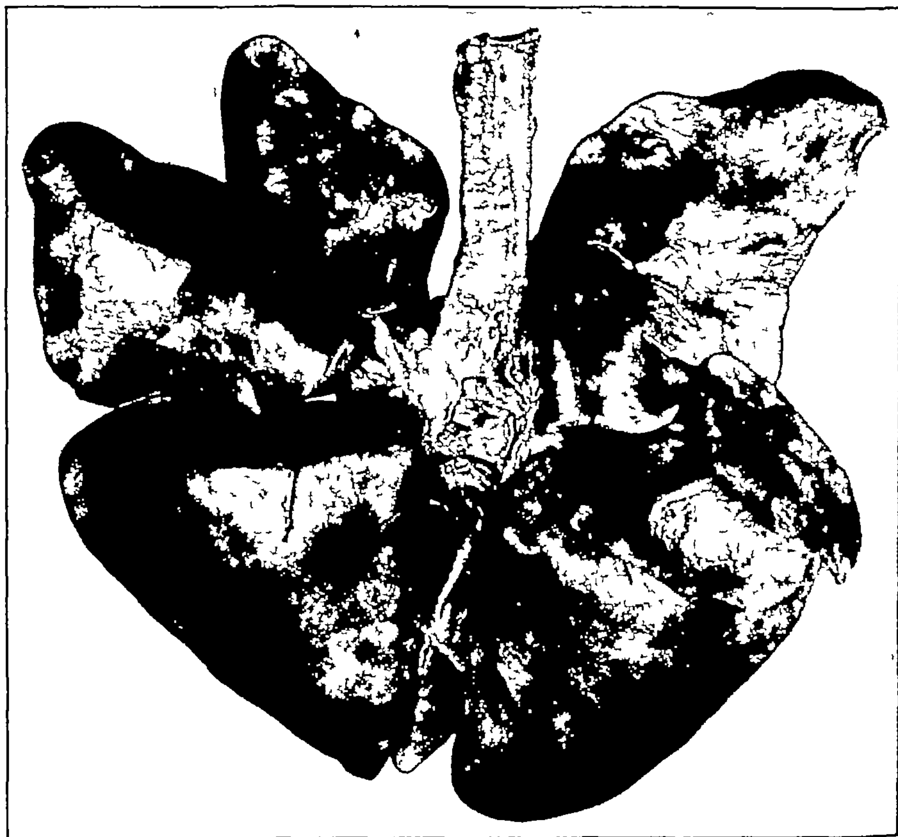


FIG 8 —Photograph of lungs of a dog after death by shock produced by autolysis of tissue *in vivo*

Subsequently shock was induced in a large series of animals, including dogs, cats, guinea pigs, rabbits, and rats, for determining the effects of various types of treatment In these experiments, tissue pulp of muscle, liver and kidney from animals of the same species, was implanted as described Hemoconcentration was used as the indicator of the circulatory deficiency The same pattern of congestive, edematous and hemorrhagic changes, as described above, were present in the viscera in these series

In other groups of dogs, shock was induced by burns and by injecting various substances which had been found by other

Fig. 9 — Photomicrograph of lung after death by shock. Note the engorgement of the capillaries and venules and the numerous minute hemorrhages.



Fig. 10 — Photomicrograph of kidney from a dog after death by shock. This shows capillary hyperemia and acute granular degeneration of tubular epithelium.

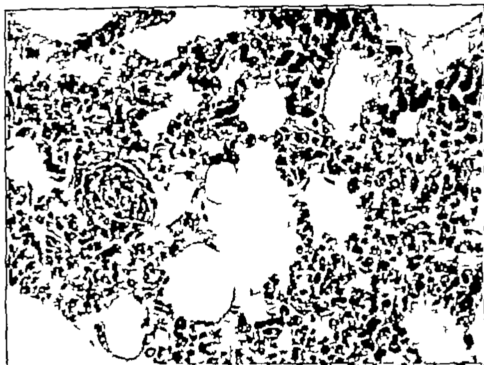


FIG. 9 — Photomicrograph of lung after death by shock. Note the engorgement of the capillaries and venules and the numerous minute hemorrhages.



FIG. 10 — Photomicrograph of kidney from a dog after death by shock. This shows capillary hyperemia and acute granular degeneration of tubular epithelium.

investigators to produce this effect The substances included histamine, peptone, extracts of muscle, of liver and of intestinal mucosa, bile, sodium glycocholate and horse serum, both in sensitized and in non-sensitized dogs In every instance, with the exception of horse serum in non-sensitized dogs, the injections resulted in severe illness of the same type which followed the implantation of tissue pulp Hemoconcentration occurred regularly and promptly When the animals recovered, the hemoconcentration subsided When death resulted, the postmortem findings were identically the same as found in the experiments already described

In one group of experiments, a neutralized solution of trypan blue, pH 7 6, was injected intravenously when examinations of the blood indicated that hemoconcentration was developing Extensive visceral areas were found at necropsy to be stained with the dye These included the lungs and pleuræ, the pericardium, the mucosæ and the linings of the gall bladder, the renal pelves and the bladder Likewise the serous effusions in the pleural and pericardial cavities were distinctly tinged with blue The muscles and other peripheral tissues were not affected

These results indicate that capillary endothelium in extensive visceral areas became abnormally permeable to colloids The permeability and the loss of fluid were not limited to the area of tissue injury This finding is incompatible with the belief that shock is due to loss of fluid in local areas of trauma

Morphologic Changes in Clinical Shock.—Postmortem observations were made after fatal shock resulting from operative procedures and from other causes The following instance is typical

A white woman fifty-four years of age had been prepared for colonic resection by a previous colostomy operation The resection under ether anesthesia was begun at 8 00 A M and was finished in thirty-five minutes The patient's condition as indicated by pulse, respiration and blood pressure, was satisfactory when the operation was finished The blood pressure was not only well maintained, it actually increased for several hours, so that at 6 00 P M it was at its highest point Meanwhile hemoconcentration had developed steadily (see Chart 4) The erythrocytic count rose from 3,720,000 before the operation to almost 6,000,000 nine hours later—a concentration of more than 60 per cent The concentration of the blood three hours after the operation forecast the impending circulatory collapse twelve hours before compensa-

tion failed Death occurred by shock twenty-six hours after the operation

Necropsy examination showed cyanotic congestion and edema of both lungs (see Fig 11) This was diffuse in distribution but was more intense in the posterior portions. There was blood tinged serous fluid in the pleural and peritoneal cavities The area

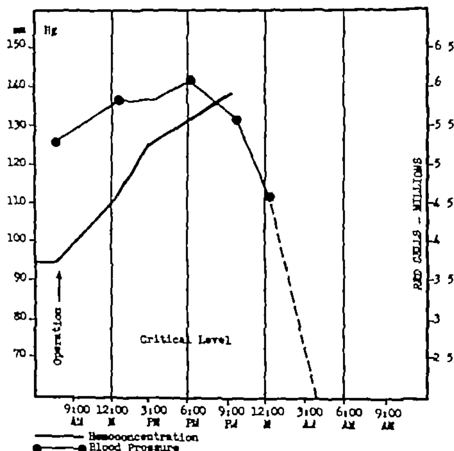


CHART 4 —This records the blood pressure and hemoconcentration during the development of postoperative shock (colonic resection) Hemoconcentration, evident in three hours after the operation, had reached 40 per cent in nine hours at which time the blood pressure was at its highest point

of surgical operation was not more congested and edematous than elsewhere and there were no gross hemorrhages The intestinal mucosa was swollen and had a purplish cyanotic color The parenchyma of the liver kidneys pancreas and adrenals was more hyperemic than normally The spleen was flabby and its capsule wrinkled There were petechial hemorrhages in the pericardium and in the pleurae

Microscopic examination revealed diffuse congestion and edema

of the lungs (Fig 12) and of the serosæ and mucosæ of the pulmonary and gastro-intestinal tract There were capillary hemorrhages in these tissues and in the kidneys The myocardium, liver and kidneys showed parenchymatous degeneration Minute areas of recent necrosis were found in the liver, spleen, kidneys



FIG 11 —Photograph of lung after postoperative shock Both lungs were diffusely hyperemic and the pleural surfaces contained numerous petechial hemorrhages

and lymph nodes The splenic pulp contained less than the usual amount of blood The capillaries and venules in the liver, kidneys, adrenals and pancreas were abnormally distended with red corpuscles

Exactly the same pattern of circulatory changes was found at necropsy in other cases of surgical shock and of shock resulting

from burns, from poisoning (mercuric chloride, sedormid, arsenicals), eclampsia, obstetrical shock, serum disease hemorrhagic pancreatitis, intestinal strangulation, mesenteric thrombosis rupture of viscera, and from severe bacterial and metabolic intoxications The occurrence of the shock syndrome in these conditions will be discussed in subsequent chapters

I was granted permission by the United States Surgeon General to examine files of necropsy records made by the medical officers of the A E F in France during the World War I Records of cases in which wound shock had resulted fatally, contained

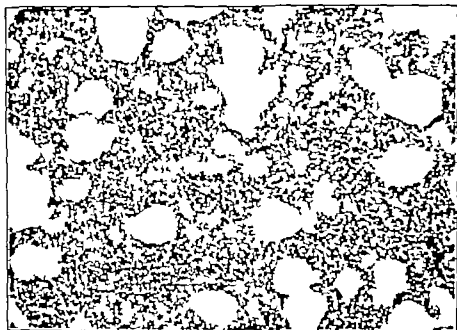


FIG. 12.—Photomicrograph of lung shown in Figure 11 Marked capillo-venous hyperemia capillary hemorrhages and moderate edema are shown.

descriptions of congestive and edematous conditions of the viscera exactly like those given in the preceding paragraphs. Frequently the phrase wet autopsy was used to denote the contrast between these and the 'dry autopsy seen when hemorrhage had been the chief cause of death The officers who made the examinations did not comment on any possible relationship between the changes described and death by shock. In accordance with prevailing custom the circulatory changes were designated as "acute passive congestion and edema.

Characteristic Pathologic Changes.—Attention was first called in 1932 to the observation that the syndrome of shock is accom

panied by significant morphologic changes which are related etiologically to that syndrome That observation has been confirmed by others and no invalidating evidence has appeared in the intervening years The morphologic features seen at necropsy after death by shock fall into two groups (*a*) those which have a direct causative relationship to the mechanism of the circulatory disturbance, and (*b*) those which are regarded as secondary or as resulting from inefficient circulation

A **Direct Effects** —The gross and microscopic evidences of endothelial damage belong in the first group These have been published in detail several times (288[3,6,7,8,9]) They may be summarized as follows The superficial veins are collapsed and bloodless The blood in the heart and large vessels and in the parenchyma of organs is dark and thick and has failed to clot Frequently it has a deep purplish cast The serous surfaces are diffusely hyperemic and appear cyanotic In severe cases, they contain ecchymoses and the cavities contain blood-tinged fluid The wall of the stomach is relaxed, and minute hemorrhagic flecks usually can be seen in the mucous lining Frequently the latter is diffusely congested, particularly in the pyloric end The fluid in the stomach usually contains brown flocculi, the significance of which as derived from capillary hemorrhages has already been discussed The bowels are atonic, relaxed and distended, the minute vessels along the mesenteric attachment are engorged and prominent The mucosæ are congested, edematous and frequently contain ecchymoses, their appearance resembles purple velvet and occasionally there is bloody fluid within the lumen of the bowel

The lungs are deeply congested either diffusely or in areas, producing a mottled appearance Microscopically, the capillaries are distended and the venules are dilated and packed with corpuscles Hemorrhages from the capillaries are numerous and marked edema is seen, particularly if death has been delayed somewhat The edema fluid has a high protein content and its specific gravity approximates that of the blood plasma The meninges are hyperemic, their capillaries and venules are dilated Frequently capillary hemorrhages are seen both in the pia-arachnoid, the choroid plexus and in the white substance of the brain

The liver and kidneys are deeply congested Blood oozes and drips from the parenchyma when this is sectioned Patches of hemorrhage from capillaries occur in the renal medulla, and numerous red cells are observed within the tubules in such areas

This is an obvious source for the hematuria that may be detected clinically

Microscopic amounts of serous fluid are seen in the intercellular spaces of visceral tissues such as liver, kidneys mucosæ, pancreas and adrenals This finding in shock arising from various causes was emphasized by Eppinger under the title *Die seröse Entzündung* It was explained as originating by leakage of plasma through abnormally permeable endothelium His reasons for avoiding the term *edema* as descriptive of this change, are not apparent.

The spleen usually contains less blood than it does normally In dogs it is firm contracted and dry The human spleen is flabby and the capsule wrinkled but it is not so contracted and bloodless as in dogs Apparently the human spleen is not so well supplied with musculature as that of dogs, hence it contracts less effectively The heart has a purplish cyanotic color and there is engorgement of the venules and capillaries in the myocardium The adrenal glands participate in the capillary congestion seen elsewhere Frequently there is vacuolization and shrinkage of the cortical cells which has been described by Zwemer and by Selye as resulting from a physiologic demand for cortical hormone

Pigmentation of hematogenous origin may be seen in the lungs, liver, kidneys and spleen when death from shock has been delayed twenty four hours or longer It results from the hemolysis of extravasated erythrocytes and is not a feature when death occurs early

The congestive edematous and hemorrhagic changes described are indicative of capillary atony and endothelial damage They are found in the visceral not in the somatic areas It is possible that the selective distribution of blood favoring vital organs at the expense of the periphery is responsible for the fact that neither capillary engorgement hemorrhages nor edema is found in the peripheral tissues

We have noted that evidences of circulatory disturbance are more marked in some visceral parts *e g* the respiratory tract than in others. This is not constant occasionally the abdominal viscera are relatively much more congested than the thoracic We have observed this particularly in dogs after injections of proteoses and after anaphylaxis

In short the visible circulatory disturbances characteristic of shock are seen in the viscera of the cranial thoracic and abdominal cavities. The degree of change varies in these regions but tends to be more marked in the respiratory tract

B **Secondary or Associated Effects** —The most important associated changes found were acute parenchymatous degeneration of the liver, kidneys and myocardium and areas of necrosis in these and in other tissues The parenchymatous or granular degeneration was sometimes slight, sometimes marked It was evidenced by the usual slight pallor and swelling of the organ, except when the pallor was overshadowed by congestion, and by fine granulation and vacuolization of the cytoplasm seen microscopically When death has been delayed twenty-four hours or more, the renal tubules are distended and may contain débris

Necrosis of hepatic cells was noted in about 20 per cent of the experimental animals and was seen frequently in human cases Usually the necrosis involved cells about the central veins, but frequently there were focal necroses of small size and irregular distribution like those seen after death from severe acute infections or intoxications In a few instances there were extensive massive necroses of the liver and of renal cortex like those seen after death from certain poisons as cincophen or cantharides Focal necroses occurred frequently also in lymph nodes, spleen, pancreas and adrenals, both in cortex and medulla, in man and in animals They were found occasionally in the myocardium in human cases but so far we have not seen them in the myocardium of animals

We have not as yet devised a method of showing what relationship exists between these degenerations and necroses and the mechanism of shock We have suspected that the parenchymatous degeneration may be related to anoxia which is a marked feature in the terminal stages of shock But the occurrence of focal areas of necrosis is as inexplicable here as in other conditions where they are found

Small scattered areas of atelectasis were often found in the lungs At first we regarded these as artifacts produced by pressure in removing and sectioning the lungs, but they were found later when precautions had been observed to prevent such accidental collapse I have no hypothesis to offer regarding the origin of this feature

Both the secondary changes and those described as indicative of endothelial damage vary in their severity and in their distribution These variations appear to depend, not on the causative agent itself but on some factor of susceptibility in the individual The degree of morphologic change and its distribution in different tissues was found to vary even when animals of the same species were subjected to the same technique for producing shock This

statement applies also to shock occurring from the same cause in human subjects.

Gastric Ulcers.—A significant associated pathologic feature is the occurrence of gastric or duodenal ulcers in cases of shock with delayed death A classical instance is Curling's ulcer developing after burns. Harkins recently reported such a case and cited more than 100 instances from the reports of others. This complication usually develops several days or weeks after the burn However in severe burns with early death there are ecchymoses in the gastro-intestinal mucosæ. It is probable that these are the initial lesions which in some cases may not heal but may develop into true ulcers.

McIlroy (1928) reported on acute gastric ulcers in cats which had received large doses of histamine by injection Buchner, Liebert and Molloy reported similar lesions in rats after injections of histamine

Selye reported that the formation of gastric and intestinal erosions is a characteristic morphologic feature in shock produced experimentally in rats by injections of drugs, exposure to cold and by other means Frequently these erosions developed into true ulcers. "The gastric and intestinal ulcers appeared histologically to be due to complete dissolution of the mucosa and are often accompanied by inflammatory infiltrations in the submucosa and muscularis. Perforating gastric ulcers have repeatedly been observed, they led to abscess formation in the peritoneal cavity in the immediate vicinity of the perforation"

Mann (1916) found ulcers in the gastric mucosa of dogs and cats after adrenalectomy These apparently developed at the site of minute local hemorrhages in the mucosa Subsequently it was shown that animals lacking adrenal cortical hormone will develop shock gradually but regularly (see Chapter XVI) and the occurrence of gastric or intestinal ulcers was noted repeatedly after adrenalectomy Banting and Gairns (1926) reported this observation and Rogoff and Stewart (1926) found ulcers in the stomach or duodenum in about 20 per cent of the dogs in a large series of such experiments This feature was noted subsequently by several other workers

It is known that cincophen poisoning may produce extensive hepatic necrosis like that seen in "acute yellow atrophy" of the liver Van Wagoner and Churchill were studying this effect experimentally in dogs and found incidentally that gastric ulcers developed in 24 out of 30 animals in chronic cincophen poisoning

This finding has been confirmed repeatedly and it has been shown that the same effect follows when the drug is administered parenterally, hence the ulcers result from a systemic rather than from a local action of the drug Acute cincophen poisoning is accompanied by many of the signs of shock It has not been shown whether this systemic disturbance of circulation results from the direct effect of the drug upon endothelium or whether from the absorption of products from the extensive damage to the liver

Penner and Bernheim made observations on 47 instances of acute ulcers in the upper digestive tract in human beings Detailed postmortem studies were made in many of these The ulcers occurred as complications or sequelæ of various clinical conditions such as extensive surgical procedures (thoracotomy for pulmonary gangrene and abscess, cholecystectomy, prostatectomy, laminectomy and intracranial operations), acute peritonitis, diabetic acidosis, burns, freezing and other grave systemic disorders

They noted that all these cases had in common the factor of shock and that this is accompanied by arteriolar constriction as a characteristic vascular response If vasoconstriction is of sufficient degree and duration it will cause local ischemia followed by edema and necrosis The action of digestive juices promptly causes ulceration in such an area, the authors believed that the local ulcerations resulted by this mechanism Klemperer and these authors made another report on this condition which they reproduced in rabbits, guinea pigs, dogs and cats by administering adrenalin intraperitoneally They stated that the lesions found in these experiments were histologically like those of acute ulcers seen in man

It is possible that gastric mucosal ulcers result from maximal arteriolar constriction as described by these authors It is also possible that they develop from ecchymoses in the gastric or duodenal mucosa Erosions of these, produced by peptic digestion, might give rise to the lesions described

Summary —Our observations on visible circulatory changes accompanying shock corroborate and confirm those recorded by others The same pattern of diffuse capillary congestion, edema, effusions and petechial hemorrhages was found in the viscera after shock produced experimentally by various means and in clinical cases of shock arising from various causes

These changes are related directly to capillary atony and to the mechanism by which the disturbances of circulation developed When death followed the implantation of tissue substance in the

peritoneal cavity, the visceral appearances were the same as after the injection of a lethal amount of histamine, of peptone or of tissue extract

These findings confirm the conclusions resulting from investigations on capillary physiology (Chapters I, IV, VI) It appears that absorption of substances resulting from the autolysis of normal tissues, will cause atony of capillaries in extensive visceral areas This is accompanied by hemoconcentration and by evidences of circulatory deficiency culminating in the syndrome of shock. If the disturbance is of sufficient degree, death by circulatory failure results.

Parenchymatous degeneration and necrosis are found in various organs after death by shock. Scattered small areas of atelectasis occur frequently in the lungs The relationship of these associated changes to the mechanism of shock is not apparent

Shock with delayed death occasionally is accompanied by ulcers in the mucosa of the stomach and duodenum These may result from arteriolar vasoconstriction of such degree as to cause anemic necrosis of the mucosa or they may develop from local ecchymoses.

Like other conditions of disease shock is accompanied by a characteristic pattern of visceral changes which are etiologically related to its mechanism of origin This finding invalidates the belief that shock is not accompanied by significant morphologic changes.

The occurrence of capillary dilatation stasis, edema serous effusions and petechiæ in regions remote from the area of injury, does not support the supposition that this form of circulatory deficiency is due to loss of blood and fluid *locally* at the site of injury But these features corroborate the explanation that shock results from the effects of injurious agents upon the endothelium of capillaries and venules in systemic areas

CHAPTER XII

EFFECTS OF BURNS, HEAT AND RADIANT ENERGY

BURNS

Physiologic and Pathologic Features —The systemic reaction to extensive superficial burns[1] of the skin forms a characteristic picture The pulse is rapid and weak, the respirations are rapid and shallow and the blood pressure declines progressively Thirst is marked but drinking is followed by vomiting of fluid which frequently contains traces of blood The temperature at first is sharply elevated but it may decline as death approaches The skin, in areas remote from the burn, becomes cold and clammy There are clinical signs of pulmonary congestion and edema The urine is scanty or suppressed, it is dark in color and contains hemoglobin and traces of albumin Bloody diarrhea may be present The mental state is disturbed "The patient becomes delirious or stuporous, but extremely restless, and finally passes into coma which ends in death The pulse is small, respiration rapid and shallow, and the blood pressure sinks, producing the whole symptom-complex of shock, such as follows great trauma" (MacCallum, p 363)

Characteristic abnormalities in the morphology and chemistry of the blood develop after burns The erythrocytic count increases sharply and the degree of hemoconcentration is proportionate to the severity of the burn Tappeiner (1881) recorded 4 fatal cases in which the counts of erythrocytes, taken from six to seventeen hours after the accident, ranged from 7 810,000 to 8,960,000 per cmm Wilms (1901) reported 6,900,000, 6,500,000, 6,700,000 and 7,200,000 red cells per cmm respectively, in 4 cases Two cases, ending fatally within a few hours, had red cell counts of 8,200,000 and 8,000,000 respectively Locke (1902) reported erythrocytic counts of 9,000,000 or more in 5 out of 6 fatal burns The highest count found in 4 non-fatal burns was 7,266,000

Underhill and associates made detailed examinations of the blood in 15 cases seriously burned The hemoglobin in these

[1] Burns, scalding, electricity, caustics and chemicals when applied to the skin produce systemic effects which are similar

ranged from 149 to 209 per cent of normal The concentration of the blood was less in mild cases and appeared to vary with the severity of the burns Underhill stated that neither man nor animals can survive hemoconcentration of 140 per cent and that the condition becomes precarious when the hemoglobin rises to 125 per cent. "Marked concentration of the blood means a failing circulation an inefficient oxygen carrier, oxygen starvation of the tissues, fall of temperature (and blood pressure) and finally, suspension of vital activities" Pack assigned the hemoconcentration to increased permeability of the capillary walls caused by the action of the "burn toxin" on the capillary endothelium, resulting in leakage of fluid into the tissue spaces

A marked leukocytosis occurs after burns. Bardeen (1897) mentioned this as a characteristic finding Locke found that a marked leukocytosis appeared within an hour and that it was progressive and proportionate to the severity of the burn The counts ranged between 10 000 and 50 000 within two-and a half hours after the accident In one case a count of 78,000 leukocytes was found within thirty minutes after the burn was received The count was above 50,000 before death in each of the fatal cases Such leukocytosis cannot be attributed to infection since it occurs immediately after the injury Many others have substantiated these findings. A marked leukocytosis occurs also after extensive physical trauma such as shell fragment wounds or crushing injuries to the limbs These facts suggest a kinship in the mechanisms by which the leukocytosis is produced If the physiologic disturbances incident to burns are compared with those of traumatic or experimental shock they are found to coincide in a remarkable fashion

Underhill and associates found the non-protein nitrogen creatinin urea and sugar content of the blood above normal limits after burns In a series of 10 cases the non protein nitrogen ranged from 30 to 60 mg per 100 cc The sugar content was increased by about 30 to 50 per cent and the blood chlorides were below normal They noted that the blood chlorides seemed to vary inversely with the concentration of the blood as indicated by its hemoglobin content Oliguria occurred regularly and the urine contained hemoglobin and albumin They explained impairment of renal function as due to concentration of the blood The changes in the chemical composition of blood noted by Underhill have been confirmed by others They are essentially the same as in shock from other causes (Chapter II)

The congestive, hemorrhagic and edematous visceral appearances after extensive burns are of the same pattern as those found after traumatic shock, anaphylaxis and anaphylactoid reactions Cumin (1823) and Long (1840) reported congestion of the viscera, engorgement of the lungs, hemorrhagic spots in serous and mucous surfaces, and fluid in serous cavities as the prominent features These findings have been confirmed and elaborated by Schjerning (1884), by Bardeen (1897), by Wilms (1901), by Pack (1926) and by many others I have had occasion to make postmortem examinations after death from burns in a number of cases These confirmed the observations of the authors cited The morphologic changes were of the same character as those found after death by shock from other causes (Fig 13)



FIG 13 —Photograph of a lung after death from cutaneous burns A lung of normal color (right) is shown for comparison

Pathologic Physiology —The clinical and morphologic changes as indicated in the preceding paragraphs, have been confirmed repeatedly by subsequent writers They have been reviewed well by Harkins (1938) and subsequent reports were analyzed by Lam (1941) The latter gives justified emphasis to the disturbances of fluid balance and of electrolytic concentrations which result from burns Both the morphologic and the chief chemical features described are substantiated in a recent report by Tenery These appear identical with those which accompany shock from other causes (Chapters II, III, and VII)

The major item in which these reports differ pertains to the chlorides of the blood, most investigators report a decline, some found little change and a few found the blood chlorides slightly

increased One factor which probably accounts for these varying results, is that some authors made determinations for chlorides on the *whole* blood, others on the *plasma or serum* some did not specify which method was used In the shift of electrolytes which occurs when cells are affected deleteriously by anoxia or other causes NaCl passes from the region of higher concentration—the plasma— to that of the lower—the cells. Such a shift between the *plasma* and the *erythrocytes* would not affect the *total* sodium chloride content of the blood it would be evident only if the plasma and cells were analyzed separately In concentrated blood, much plasma having escaped by leakage, the chloride content of the whole blood may be high because of the increased chloride content of the erythrocytes, yet the plasma chlorides may be decreased Lowden and associates made such observations after burns the chloride content of the plasma was *below normal* but that of the whole blood was *increased* These considerations apply likewise to analyses for electrolytes in shock from other conditions.

A survey of the findings recorded by many writers indicates that the following changes usually, but not always, are found after severe burns a decrease in the total blood volume, hemoconcentration and leukocytosis a disturbance of fluid balance accompanied by a shift of fluid from the blood to the tissues a shift of electrolytes from regions of higher to those of lower concentrations, resulting in an increase in the potassium calcium magnesium, phosphates and sulphates and a decrease in the sodium chlorides and bicarbonates of the plasma, a decrease in the alkaline reserve and in the normal ratio of albumin to globulin, an increase in the sugar and a progressive rise in the non-protein nitrogen of the blood The coagulation time is shortened at first, then greatly lengthened

Decreased renal elimination occurs promptly after severe burns, there is oliguria or anuria the urine contains albumin and the specific gravity is high its content of chlorides is decreased and in later stages acetonuria may appear (Pack and Davis)

The low chloride content of the blood, the increased non protein nitrogen the decreased A/G ratio, and the deficient renal elimination are progressive they are more prominent two or more days after the burn

A highly significant feature after severe burns is the extensive damage suffered by the liver This ranges from parenchymatous degeneration with numerous focal or mid zonal necroses, to extensive necrosis affecting most of the lobules This effect has

been recorded repeatedly from the time of Schjerning (1884) to the present. Harkins observed that deaths within forty-eight hours are due to shock, fatalities occurring forty-eight to one hundred and twenty hours after the burn are liver deaths, and in those after ninety-six hours infection is the chief factor. Any acceptable explanation of the mechanism by which burns affect the system, must explain the origin of this extensive damage seen in hepatic, renal and other tissues remote from the injury.

Belt reported the necropsy findings in 4 fatal cases, these included acute degeneration of the myocardium, liver and kidneys, weeping hemorrhages of mucous membranes particularly in the stomach and renal pelves, and hemorrhagic congestion of the lungs. Voluminous peritoneal effusion was found in one case. The livers contained extensive necroses, hyaline condensations and nuclear inclusions indistinguishable from those seen after death by yellow fever. He believed "Some toxic substance capable of profoundly harmful effects is undoubtedly elaborated in the damaged tissue."

Buis and Hartman recently published pathologic studies especially of the liver after superficial burns in man and in animals. The livers were large, light yellow in color, greasy and friable in consistency, and sometimes contained visible hemorrhages. The lobular markings were abnormally conspicuous. Microscopically there were varying degrees of acute degeneration and necrosis ranging to extreme degrees comparable with acute yellow atrophy. Degeneration occurred also in the kidneys and in the brain.

Shock, accompanied by loss of plasma and by hemoconcentration occurred regularly. Visceral congestion was associated with the parenchymatous degeneration seen in the organs. The authors believed that anoxia was a contributory cause for the extensive damage seen in the liver and elsewhere.

A Toxic Factor.—The chief controversial item in discussions on burns is the same as in those on traumatic shock, *i.e.*, the part played by toxic products absorbed from the injured tissues. Most writers in past decades have explained the symptomatology of burns on this basis, and numerous biochemical substances have been proposed as the specific "toxin" (see reviews by Pack and by Harkins). Prominent among the substances incriminated were urea, hemolysins, guanidine, proteoses, peptone, unspecified protein cleavage products, toxalbumin and the like. Failure to support any of these hypotheses by acceptable evidence, naturally brought the theory of a "burn toxin" into question. Underhill and Kapsinow stated: "Our experience with burns leads us to doubt

the existence of a 'burn toxin' and to believe that the persistence of this viewpoint is an obstruction in the way of clarification of the burn problem ' Some believe that Underhill s attitude while admirably conservative, has not contributed to clarification of this moot point

The chief evidence opposed to the theory of intoxication, is negative rather than positive in character Underhill and associates showed that the absorption of substances injected subcutaneously in burned area was retarded But Mason and associates found no delay in the absorption and excretion of sodium iodide under similar conditions. Let it be recalled that the mechanism of fluid balance and of absorption is seriously deranged when shock has developed Perhaps the animals tested by Underhill were in more advanced shock than those in Mason's tests

Experiments by Harrison and Blalock failed to show intoxicating effects from the transplantation of burned skin from one animal to another, beneficial effects from the débridement of the burned area or toxic effects by transfusion of blood from burned dogs to normal ones However, Blalock stated subsequently (47*) "It is my impression that toxins have not been excluded as important agencies in the causation of ill effects following burns.

Blalock, Harkins their associates, and many others have believed that the loss of fluid from the blood into and about the burned area is the chief factor causing disturbance of the circulation None will question that such loss is an important factor—important in proportion to the volume of fluid lost But local loss of fluid alone does not disturb systemic fluid balance So long as that mechanism is functioning physiologically loss of fluid locally is compensated by absorption of fluid from other tissues and from the gastro-intestinal tract. Voluminous local accumulations of fluid as ascites pleural effusions or anasarca do not produce the syndrome of shock, neither do they cause anything resembling the visceral hepatic and renal changes which accompany burns. Those changes are not explained adequately on the basis of *local* loss of fluid

A significant bit of evidence was derived from animals joined in pairs by surgical anastomosis of the lateral abdominal walls After the healing of the tissues, such parabiotic animals are suitable for testing toxic effects substances introduced parenterally in the one, will reach the circulation of the other Vogt published detailed protocols of 83 experiments performed on such animals.

When one of the parabiots was severely burned, the uninjured one developed symptoms like those of its mate and died with the same signs of intoxication Death of the animal not burned was prevented by the surgical separation of the parabiosis shortly after one of the pair had been burned If surgical separation was delayed too long, both animals died Such results are difficult to explain except on the basis of toxic substances absorbed from the burned areas and distributed *via* the blood stream

Harkins, Wilson and Stewart compared the effects of protein-free extracts of normal skin with those of burned skin prepared by the same method, both contained an apparently identical depressor substance This was interpreted as evidence against the theory of a "burn toxin " However, this result does not appear to invalidate that hypothesis Harris found that extracts of normal human skin contain a substance which caused wheals when introduced intradermally, caused contraction of perfused guinea pig uterine muscle and produced a fall in blood pressure when given intravenously A comparison of a similar substance found in animal skin showed its presence in equal quantities in normal skin and in skin removed *immediately* after burning or freezing But the concentration of it decreased progressively in samples of burned skin taken after intervals of time This fact suggested the progressive absorption of the substance from the burned area into the animal's body

Barsoum and Gaddum compared the blood histamine of normal subjects with that of 9 persons severely burned A marked elevation in the latter, amounting to 5 times the normal, was found during the first week after the burn Rosenthal tested the blood of shoats, dogs, guinea pigs and of human beings for the presence of histamine-like substances after severe burns of the skin He found that the blood of each species contained a substance which caused contraction of virgin guinea pig uterine muscle This substance differed from histamine in that it was shown to be thermolabile

A number of investigations are on record tending to show that injurious or toxic substances are formed in tissues damaged by heat Wilson and his co-workers made experiments of a different type from those referred to They separated a large area of rabbit's skin from the underlying tissues in order to collect larger volumes of the fluid which distends tissues adjacent to burns The skin was then severely burned and the edema fluid which collected beneath it was injected into other rabbits Sometimes

death occurred within a few seconds after an injection of 3 to 5 cc of this fluid In other instances the rabbits developed muscular weakness labored respiration, increased pulse rate, pallor of the ears and dilatation of the pupils, sometimes urine and feces were voided The temperature first rose, then fell, the blood pressure declined and death occurred one to five hours after the injection That the circulatory failure was not of cardiac origin was demonstrated by clamping the aorta immediately the pressure rose from the level of 30 mm to 112 mm Hg This was interpreted as indicating that the myocardial function was not seriously impaired.

There was a progressive increase in the toxicity of the edema fluid as time elapsed after the burn Specimens taken after twenty four to forty-eight hours produced more severe effects than those taken shortly after the burn Filtration to remove bacteria did not remove the toxic property "The gradual development of toxicity of edema fluid in the absence of bacterial growth strongly suggested that autolysis of injured tissue was responsible for toxin formation ' Heating the edema fluid lessened its toxicity, as was observed by Rosenthal Marked degeneration of hepatic cells was another point in common between their results and the effects of burns in human cases.

The most extensive experimental work on burns reported in recent years is that of Christophe (1939) Observations were made on 164 dogs and the text of the report exclusive of protocols, photomicrographs, etc., covers 85 pages Studies were made on biologic phenomena accompanying burns with particular reference to delayed effects.

Signs of 'nephritis' developed early, there was oliguria or anuria for twenty four to forty-eight hours The urine contained albumin pigment débris and casts The non protein nitrogen of the blood increased progressively, the blood urea level was elevated by 100 to 400 mg per cent (see Chapter XV) Marked visceral edema developed, the fluid of which was rich in albumin The osmotic pressure of the plasma decreased and the A/G ratio was reversed The reserve alkalinity declined and acidosis, as indicated by pH 7 44 to pH 7 33, developed. The plasma chlorides declined while those of the tissues increased. The total blood volume decreased about 50 per cent in some cases, there was an increase in the blood cholesterin

The reader should thoughtfully compare these changes with those of the shock syndrome as detailed in Chapters II, III and IV

In one series of experiments the entire skin surface of the hind leg was thoroughly burned, limbs were then amputated at the hip after the lapse of varying periods of time If such amputations were done within six hours after the burn, the animal lived, if done six to ten hours after the burn, death followed

In other experiments, the hind limb of a normal dog was disarticulated and quickly grafted to the neck of another, by anastomosing the femoral artery and vein to the external carotid artery and jugular vein, respectively Heparin was used to prevent clotting After circulation was shown to be established, the skin of the grafted limb was thoroughly burned with a Bunsen flame The dogs on which such experiments were made died after manifesting illness like that of burned animals, the physiologic changes likewise were similar, including a decrease in the plasma chlorides, an increase in the non-protein nitrogen and the appearance of albumin and casts in the urine

This experimental procedure excluded nerve impulses from the burned area as factors, the only connection between the normal dog and the burned area was *via* the circulating blood These and similar experiments led the author to conclude that some toxic substance, conveyed by the blood from the area burned, was responsible for the results "The progressive lethal phenomena manifested are due to the presence of a toxic principle within the blood returning from the burned area The absorption of this principle occurs within the first ten hours and the other phenomena follow with fatal outcome "[1]

In another group of experiments the author made arterial and venous anastomoses by which the *head* of the normal dog was perfused with blood from the burned dog Similar results followed, accompanied by oliguria, azotemia and death as by renal deficiency Examination of cerebral tissues in such animals showed degenerative changes like those in animals after fatal burns The region affected particularly was the anterior hypothalmus Hyperchromatic granules, vacuolization, fragmentation and disintegration were described as marked These changes were adequately confirmed by photomicrographs

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findings and the progressive increase in the non protein nitrogen of the blood to this effect The photomicrographs of the renal lesions are not distinctive of acute glomerulo-nephritis but might be interpreted as acute glomerular congestion and tubular degeneration We have seen similar renal effects frequently after death by shock from various causes. Data on other visceral changes were not published. Christophe believes that toxic substances, absorbed from burned areas, affect primarily the *brain* and that other visceral changes result through disturbed neurogenic influences This interpretation may be questioned, it seems equally probable that the cerebral renal, hepatic and other systemic effects, all result from the same noxious influences.

The evidence presented in this section has not been questioned nor controverted, it should be considered thoughtfully in relationship to the systemic effects which follow extensive burns of the skin

HEAT STROKE, INSOLATION

The recorded clinical and pathologic data on the effects of excessive temperatures, resemble closely those resulting from burns Heilman and Montgomery described such patients as in a condition of shock. Drinker noted these features "Dizziness headache fainting vomiting, a broad chain of symptoms such as might initiate a severe infection, characterize the onset. Sudden collapse and coma with accompanying high fever are not uncommon The pulse is rapid the blood pressure low and the breathing shallow and fast The patient resembles one in surgical shock except for the elevation of temperature" Hill stated "At postmortem, the organs of a case of heat stroke show capillary congestion as in wound shock. ✓ Le Count described visceral congestion edema of the meninges, brain and lungs, petechiæ in the viscera and skin and parenchymatous degeneration of the myocardium liver and kidneys as characteristic changes seen after death by heat stroke Willcox made similar observations on deaths from sunstroke among soldiers in the tropics. "Edema and general hyperemia of the brain and lepto-meninges were observed and cloudy swelling of the liver kidneys and myocardium was found Petechiæ of the skin and mucous membrane were seen in some cases. Pulmonary edema was a terminal event in the fatal cases In addition to these features, Ross noted that the blood is usually uncoagulated and dark and that extreme visceral congestion is seen

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Smith reviewed observations of others and contributed the results of his own studies on heat stroke He stated that the plasma chlorides, alkaline reserve and pH of the blood are decreased while the lactic acid and nitrogen content are increased He confirmed the observations of others concerning necropsy findings The blood was dark, thick and poorly clotted "Congestion, edema and hemorrhagic effusions occur in the lungs, and may be of extreme severity " Vascular congestion and petechial hemorrhages were found also in other viscera and in the brain The parenchymal tissues showed cloudy swelling and more advanced stages of degeneration Renal degeneration was particularly severe when death after heat stroke was delayed In these instances, azotemia was marked (see Chapter XV)

The pathologic changes seen after death resulting from therapeutic hyperthermia are exactly of the same pattern as seen after heat stroke (Gradwohl and Schisler, Lichtenstein, Kopp and Soloman, Wilbur and Stevens) F W Hartman emphasized the occurrence of degeneration and necrosis in brain tissues both in human cases and in dogs subjected to high temperatures in the same way In the case reported by Chunn and Kirkpatrick, there was persistent vomiting of "coffee grounds" fluid, hemoconcentration, progressive hypotension and icterus as in "acute yellow atrophy " Death occurred after four days, the small yellow flabby liver, weighing 1320 gm , was extensively necrotic G Wilson's report of 1 death from sunstroke and 3 from fever therapy emphasized petechial hemorrhages, especially numerous in the endocardium One case had 150 cc of blood-tinged fluid in the pleural cavities Other pathologic findings in these reports were like those of Le Count

Pinner and Margulis studied the effects of solar radiation on animals A comparison of the effects of different portions of the solar spectrum upon guinea pigs indicated that each portion was capable of producing lethal effects The clinical and pathological findings were remarkably uniform and did not vary with variation in the spectral composition of the radiant energy A marked acceleration of the respiration was the first sign of serious effect The rectal temperature rose to 108° or 109° F When radiation was discontinued at this point, the temperature declined to normal but the animals died usually in twelve to twenty-four hours

The subcutaneous tissues were congested and edematous The lungs showed areas of massive congestion and the pleural cavities contained bloody fluid in some instances Congestion of the

liver was marked and the kidneys adrenals and testes showed varying degrees of it. Histologically, small lobular interstitial pneumonias were seen frequently associated with regions of intense capillary congestion small hemorrhages and sub-pleural emphysema. The intestines and portions of the stomach showed massive congestion, stasis edema, local hemorrhagic infarctions and necroses. These findings suggested to the authors the effects of histamine like substances liberated in the regions injured by exposure to radiant energy

Several authors recorded blood studies in man and in animals exposed to high temperatures Hall and Wakefield exposed dogs to warm humid air in a closed cabinet for variable periods. This caused illness ending in death in the more severe cases. They found an increase in the lactic acid, non protein nitrogen, urea, creatinin sugar chlorides and calcium of the blood There was a decrease in the CO_2 combining power the serum pH and in the total serum proteins After death 'acute passive congestion and capillary hemorrhages were seen in all the tissues The liver showed changes ranging from acute degeneration to extensive necrosis like that of acute yellow atrophy Extensive parenchymatous degeneration and edema were seen in the kidneys A progressive azotemia developed in one animal which lived two weeks after the treatment It is significant that the necrosis of the liver after burns sunstroke and hyperthermia, has been described by several writers as resembling that of 'acute yellow atrophy' or that seen after death by yellow fever

Milder effects of heat produce changes in the blood like those of burns but these are transient Ferris and associates made clinical and chemical observations on 44 patients hospitalized during a period of excessive summer heat They were affected in varying degrees but all had hyperpyrexia ranging from 105° to 109° F The NaCl content of the blood was not altered significantly There was moderate acidosis and the blood was concentrated In the more severe cases the non protein nitrogen was above normal Seven of these manifested shock and each of them died soon no postmortem data were given

Talbott and associates reported blood studies on workmen affected in varying degrees by heat In 5 cases of "heat cramps," the cell volume red blood cells leukocytes sugar, phosphates calcium potassium and non protein nitrogen were increased, the bicarbonates chlorides, sodium and the pH of the serum were decreased Milder degrees of heat exhaustion showed less marked

effects All cases recovered McLain and Montgomery reported similar changes in workmen affected by heat cramps They noted hemoconcentration, increased blood sugar, and a decrease in the serum chlorides, no data on nitrogenous wastes were given

Irradiation Sickness —Long ago it was noted that the massive application of x-rays over the abdominal region produces grave symptoms in the patient These included nausea, vomiting, oliguria, bloody diarrhea, restlessness, small rapid pulse, declining blood pressure and profound prostration These symptoms resemble those of shock arising from other causes Other features, such as low metabolism, increased blood sugar and non-protein nitrogen, hypochlorhydria and decreased alkaline reserve, are also like those of shock The illness is usually delayed in onset, developing after two or three days, and death usually occurs about four days after exposure

The postmortem findings reported in both clinical and in experimental irradiation sickness, include diffuse congestion of the lungs, of mucous and serous surfaces and of parenchymatous organs, capillary hemorrhages in these tissues, parenchymatous degeneration of organs, and degeneration progressing to necrosis of the intestinal mucosa

Whipple and his associates noted that the manifestations after extensive irradiation were like those of heat burns but with this difference the latter produce illness immediately, while radiation sickness develops after a latent period They showed that radiation produced delayed necrosis of the glands and of the epithelium in the intestinal mucosa, and they ascribed the illness to the absorption of products of cellular disintegration The mechanism of this effect was like that which Whipple had shown in experiments on closed intestinal loops

We were impressed by the close resemblance between the manifestations of radiation sickness and those of shock resulting from various causes It seemed of interest to compare both the physiologic disturbances and the postmortem findings of radiation sickness with those which characterize shock Our initial experiments were arranged to duplicate closely the roentgen technique employed by Whipple The physical factors employed were 130 kilo-volts, 5 milliamperes, 2 mm of aluminum filter, and 30 cm skin target distance The output of the equipment was 72 r per minute Open field irradiation was given over the abdomen of healthy, normal dogs in amounts ranging from 1400 to 2800 roentgen units.

These amounts were given in one application divided between two abdominal areas

No effects were observed for twenty four to sixty hours after which signs of illness developed There were loss of appetite vomiting diarrhea and a decrease in the output of urine Traces of blood were seen in the urine, feces and vomitus These symptoms progressed steadily and death from circulatory failure occurred usually within twenty four hours after the onset of illness, *i e* three to five days after the irradiation There was no disturbance in the erythrocytes and hemoglobin content of the blood until the onset of symptoms. At this point hemoconcentration appeared regularly and progressed commensurately with the severity of the symptoms The hemoconcentration ranged from 15 to 30 per cent in one instance it reached 50 per cent

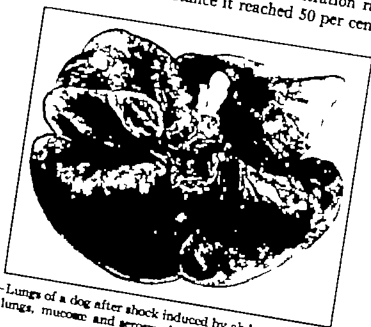


FIG. 14.—Lungs of a dog after shock induced by abdominal Roentgen irradiation. The lungs, mucosæ and serosæ show diffuse capillo-venous hyperemia

Postmortem examination showed marked diffuse hyperemia of the viscera. The lungs were mottled and cyanotic in appearance (Fig 14) Microscopic examination showed capillo-venous congestion and numerous capillary hemorrhages. The serous surfaces and the gastro-intestinal mucosæ were deeply congested. There was bloody fluid in the intestinal lumina, and the lining had the appearance of purple velvet (Fig 15) The evidences of damage were most marked in the mucosa of the small bowel. Microscopic examination showed varying degrees of degeneration and necrosis of the epithelium and marked hyperemia of the capillaries and

venules The liver and kidneys showed congestion, parenchy tous degeneration and, in some cases, necroses The spleen contracted and bloodless

In one group of 7 dogs, radiation was given over the liver, lower abdomen being protected by lead shields One of tl animals developed fatal illness accompanied by hemoconcentrat The postmortem findings were the same as described ab Another developed slight illness accompanied by 12 per hemoconcentration, but recovered The remaining dogs in group showed no hemoconcentration nor evidence of illness 2 dogs, the liver and adrenals were shielded and the irradia confined to the lower abdomen These animals manifested typ

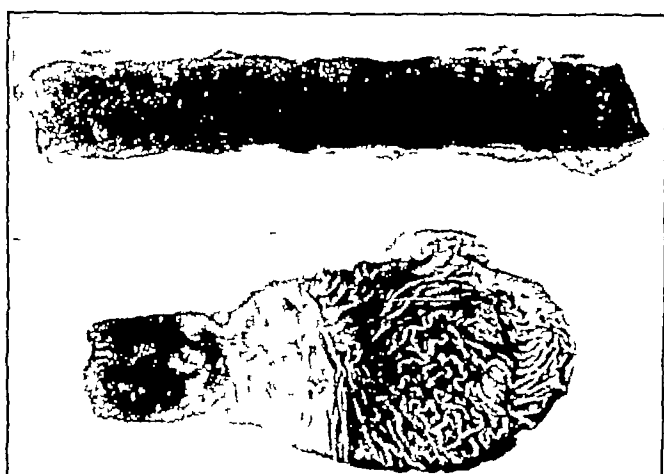


FIG 15 —Stomach and portion of small bowel after shock induced by irra tion The cardia and fundus of the stomach and the entire small bowel intensely hyperemic and contained numerous ecchymoses

reactions accompanied by hemoconcentration and followed death No illness resulted in 2 dogs which were given mass radiation over the chest These experiments corroborate observations of Whipple and of others, that the intestinal muc is more sensitive than other tissues to the injurious effects radiation

One group of dogs were treated as described, but were killed intervals of twenty-four to eighty-eight hours after exposu This was done in order to make examinations of the intesti mucosæ at earlier stages after the injury (Fig 16) Sections bowel and of other tissue were placed in fixative within minutes after the death of the dogs Study of such sections c

firmed the findings of Whipple and his associates who made similar studies. The evidences of damage were most marked in the mucosa of the small bowel The epithelium lining the crypts and covering the villi, showed all stages of disintegration and destruction Some crypts contained nuclear and cellular débris, others were empty Some of the villi retained their epithelial covering while that in the crypts showed necrosis and disintegration Other villi were completely denuded of their epithelial covering (Fig 17) Our results were concordant in 25 dogs used in this series of experiments.

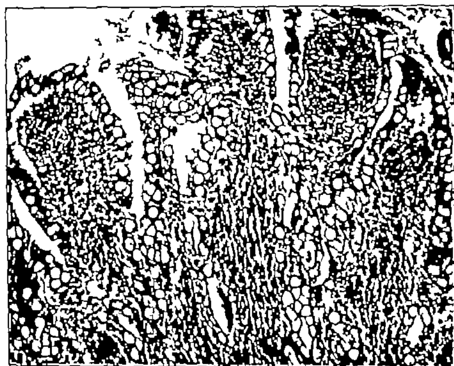


FIG. 16.—Intestinal mucosa of a dog killed twenty-four hours after abdominal irradiation. Hyperemia and marked degeneration of the lining are present.

Edsall and Pemberton interpreted radiation sickness as a toxic reaction to products of tissue disintegration Later Hall Warren and Whipple conducted extensive experiments on the subject and came to the conclusion noted earlier in this section Rolleston reviewed the various proposed explanations and found that the weight of evidence favored acute toxemia from products of cellular injury or destruction Forfota and Karady cited numerous observations on the resemblance between radiation sickness and shock They commented on the demonstrations by Ebbecke

Lewis and others, that cellular injury of any kind causes the release of H-substances which affect capillaries in the same fashion as does histamine They compared the effects of histamine and of experimental radiation in dogs and reported that chemical examinations of the blood showed the same essential variations from normal as seen in shock



FIG 17 —Intestinal mucosa of a dog killed sixty-six hours after abdominal irradiation The villi are denuded of their epithelial covering and the crypts contain débris of disintegrated glandular epithelium

Our results have confirmed those of the authors cited, also our interpretations are similar Exposure of the abdominal viscera to massive doses of roentgen irradiation causes delayed necrosis of the intestinal mucosa Absorption of cytoplasmic material from this damaged tissue seems to produce the physiologic disturbances noted The severity of the illness seems to parallel the recognizable epithelial injury The resulting symptoms are those regularly seen in shock from other causes and the condition is accompanied by progressive hemoconcentration The visceral changes seen postmortem are characteristically those of circulatory failure of the shock type

These experiments have a significant bearing on the mechanism of shock Some writers assign this to local hemorrhage and loss of

fluid, or to sympatho-adrenal hyperactivity, and disregard absorption of products from damaged tissues as a factor Injury to intestinal mucosa by radiation is like injury by heat or other physical agents, but with these differences it produces *delayed* necrosis and causes *no pain nor emotional reactions* Hence such injury eliminates hemorrhage, anesthesia, pain, emotional reactions and sympatho-adrenal hyperactivity as factors In such experiments it appears that the disturbances of circulation result solely from absorption, independent of other factors.

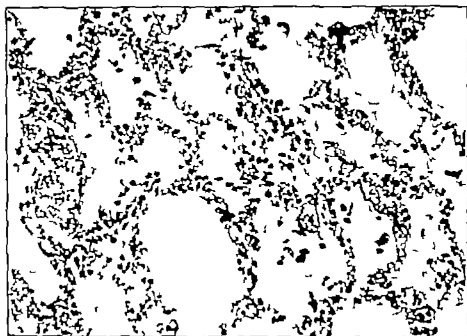


FIG 18.—Photomicrograph of human lung after death from massive x ray therapy Marked hyperemia, edema and hematogenous pigmentation are shown.

I have had opportunity to examine the tissues in only one human case of death from radiation sickness Massive roentgen therapy had been applied over the lower abdomen in the treatment of extensive pelvic carcinomatosis of uterine origin Illness began two or three days later and terminated fatally within a week The most prominent clinical features were progressive weakness and deficient renal function (see Chapter XV) Blood examinations were not made A progressive decline in blood pressure preceded death The necropsy revealed extensive necrosis of massive carcinomatous tissues in the pelvis, also of large myofibromata in the uterine wall The lungs were hyperemic

and edematous (Fig 18), as were also the abdominal viscera The mucosa of the small bowel was intensely congested and the gastric mucosa, moderately so The stomach contained "coffee grounds" fluid

Summary —The state of shock resulting from extensive burns duplicates that from trauma or from other causes, item for item These points include the clinical signs, the chemical and other alterations in the blood, and the visceral changes seen postmortem. Prominent associated effects occur in the liver and kidneys There is weighty evidence indicating that all these features are the effects of substances liberated from the damaged tissues Local loss of fluid in and about the burned area is a contributory factor but it does not provide an adequate explanation for all items in the syndrome

The pathologic physiology, clinical signs and morphologic changes which accompany sunstroke, heat stroke or excessive thermotherapy, present no points of distinction from the effects of burns The conditions mentioned are not accompanied by local loss of fluid, hence the manifestations must be assigned to the direct effects of heat upon various organs, especially the liver and the brain

Deep roentgen irradiation of the abdomen causes shock which is delayed in development Irradiation is an agent which, like heat, causes injury to tissues—particularly intestinal mucosa This is followed by delayed necrosis Absorption of the products of this injury appears to explain the delayed onset of shock Such items as pain, emotional reactions, anesthesia, hemorrhage, sympatho-adrenal hyperactivity, and local loss of fluid, appear to be eliminated as factors in shock resulting from roentgen irradiation

CHAPTER XIII

SHOCK IN OTHER CONDITIONS

SURGICAL or traumatic shock usually results from a combination of factors including absorption from injured tissues and hemorrhage Frequently the effects of anesthesia, preëxisting disease, exposure, privation or other circumstances are combined with absorption and with loss of blood. In contrast with this the pathogenesis of the same type of circulatory disturbance resulting from anaphylaxis intoxication or other disorders includes fewer factors.

Recently we have published evidence (288*) of the occurrence of shock in various conditions of disease These include anaphylaxis the effects of venoms and various poisons, extensive superficial burns intestinal obstruction pancreatitis, peritonitis and other abdominal emergencies, intoxications of metabolic or other origin, and infections of unusual severity The same type of clinical manifestations occurred in each of these conditions accompanied by hemoconcentration, and the viscera showed the characteristic pathologic features of shock The evidence referred to will be summarized briefly

Anaphylactic Shock. –This term is commonly applied to the rapidly developing illness which occurs when protein is given parenterally to an animal already sensitized to that protein Few pathologic phenomena have been so mysterious as those of anaphylaxis. Small doses of simple proteins, which produce no more effect in normal animals than would so much isotonic saline solution act like violent poisons when given to sensitized ones Some of the manifestations of this reaction have baffled investigators using every form of approach which they could devise Readers interested in details not presented here are referred to reviews by Wells, Karaner Zinsser Topley and Wilson and by Seegal

The subject is considered here because acute anaphylaxis presents all the clinical physiologic and pathologic features of shock as produced by histamine peptone or other agents, because investigators have agreed that endothelial reaction is a major factor in its mechanism and because some of its puzzling features may be clarified by an analysis of the endothelial factor

The physiologic disturbances which accompany anaphylaxis like those of shock from other causes Investigations have sho that the lactic acid, the sugar, urea, creatinin, non-protein nitro, and potassium of the blood are increased and the chloride cont decreased during anaphylactic shock The viscosity of the bl is increased and its coagulability decreased Hemoconcentrat has been noted by each who have recorded observations on t item, this appeared proportional to the apparent illness of animal The behavior of the leukocytes varies marked leu penia, as represented by a decline of 75 per cent in the numbe leukocytes, occurs in acute severe anaphylaxis while in subac or delayed reactions there is intense leukocytosis In each of th particulars, anaphylaxis and shock from other causes are in tinguishable

Congestive, edematous and hemorrhagic changes in the visc were recorded by the earliest observers on anaphylaxis Ric (1902) working with dogs noted "there is intense congestion w interstitial hemorrhages in the whole gastro-intestinal tract T lungs are congested and sometimes also the endocardium a pleura " Gay and Southard (1908) made similar observations guinea pigs Hemorrhages were most numerous in the gast intestinal tract and the lungs, but they are found also in adrenals, kidneys, pericardium, brain and meninges The auth regarded these as highly significant and emphasized that a explanation for anaphylaxis, to be acceptable, must also expl these features Similar evidences of disturbances in the min vessels were recorded by Coca (1909), Pearce and Eisenb (1910), Karsner (1912), Manwaring, Weil, Petersen and oth I have confirmed these observations in fatal anaphylactic sh in guinea pigs, rabbits and dogs Extensive hyperemia, petech hemorrhages and ecchymoses were present in the thoracic a abdominal viscera when death occurred promptly, and those sa features plus edema in the soft tissues when death was delay Exactly the same changes were noted by those who recorded appearances of the viscera at necropsy after fatal anaphylac reactions in man (Boughton, Lamson, Bullowa and Jacobi)

Evidence from various sources indicates that endothelial ce play a prominent rôle in the mechanism of anaphylaxis Cap laries lose their tonus and become abnormally permeable dur such reactions This has been shown by perfusion experime (Manwaring) and by the development of edema both in local a in systemic anaphylaxis Opie summarized the work of oth

correlated it with his own investigations and concluded that tissue cells are injured when antibody meets antigen in the tissues He interpreted the tissue edema as the effects of such injury upon capillary walls.

Petersen and his associates noted an increased flow of lymph when dogs sensitized to egg albumin received it by injection The lymph was rich in fibrin globulin albumin and erythrocytes indicating increased endothelial permeability They interpreted this as evidence that endothelium is the point of attack of the injuring agent and concluded that this effect is a primary factor in producing the symptoms of acute anaphylaxis.

Manwaring and associates emphasized the importance of liver damage in anaphylactic dogs but their final conclusion was stated as follows "We believe that the increased capillary permeability thus demonstrated will ultimately be shown to be the dominant physiologic change in protein sensitization, to which all other anaphylactic reactions are secondary" Seegal s review of the subject led to the conclusion that the symptoms of anaphylactic shock in the various animals are referable to one or the other of two causes *contraction of smooth muscle* and *increased capillary permeability* Lewis emphasized capillary permeability as the major factor and attributed it to H-substance released by tissue cells when injured by the combination of antigen with antibody

The observations cited and many others of similar import may be interpreted as follows The sensitization upon which the ana phylactic reaction depends resides not in the body fluids but in the tissue cells Sensitized cells are irritated or severely injured when an infinitesimal amount of the protein to which they are sensitive is brought in contact with them This has been shown by Opie and others The injury may be slight or marked, depend ing on the degree of the sensitization and on the dosage of the antigen When mild the irritation may be only sufficient to provoke contraction as of smooth muscle increased secretory activity of mucous and glandular cells, or severe itching and irritation of epithelial surfaces. On the other hand, the resulting injury if severe may cause extensive necrosis of the tissues. This is seen in the lymph nodes, spleen liver and other parenchymatous tissues in severe anaphylaxis also in the Arthus phenomenon of extensive necroses in muscular and subcutaneous tissues after local injections of the antigen.

The statement that tissues are injured when antigen and anti body meet within them does not exempt endothelium That

tissue is as easily damaged as any in the entire body, injury to it produces atony and increased permeability of capillary walls This fact provides the key to the observations relative to endothelial damage cited in previous paragraphs It explains why anaphylaxis produces circulatory disturbances indistinguishable from those caused by histamine, peptone or other shock-producing agents When the foreign protein is given intravenously to a sensitized animal, violent illness may develop instantly and death may occur immediately This effect is understandable as the result of severe injury to endothelium throughout the body

I have made examination of the viscera after anaphylactic death in animals and after fatal "serum sickness" in man These confirmed the observations on congestive and hemorrhagic appearances associated with anaphylaxis as seen by earlier writers The same pattern of changes are present, indicative of endothelial damage, as in shock otherwise produced These changes support the interpretation that endothelial effects are the major item in the mechanism of anaphylaxis Hepatic degeneration and necrosis occur after anaphylaxis, and some of the physiologic disturbances have been attributed to injury or dysfunction of this organ (Manwaring and others)

Anaphylactoid Reactions —A number of chemicals and poisons owe their pharmacologic action to their effects upon capillary endothelium These have been called *capillary poisons* by Heubner, Krogh and others Such substances when injected intravenously, produce reactions which are indistinguishable from anaphylaxis Hence Wells found it necessary to specify definite criteria to differentiate true anaphylaxis from such effects One requirement is that the substance must be a protein, another, that the reaction must not be produced by the first injection but must have been preceded by a sensitizing dose of the same protein Reactions which do not meet these criteria are classed as *anaphylactoid* rather than anaphylactic

Heubner's description (1907) of the postmortem appearances after injections of capillary poisons is very significant because it duplicates the characteristic pathologic features of shock The venules in the viscera were deeply congested The peritoneal surfaces of the bowels were deep red The mucosæ were dark red and contained hemorrhagic flecks Similar flecks were present in the surfaces of the liver, spleen and kidneys Blood-tinged fluid was present in the serous cavities although no visible origin for the hemorrhage could be found The lungs and pleura were

deep red and contained numerous ecchymoses Blood flowed freely from the substance of the organs when these were sectioned

Microscopically, there were marked dilatation of the venules and capillaries in all the organs and minute hemorrhages in the substance of the lungs liver and kidneys. The arterioles were maximally contracted which indicated to Heubner that vasomotor relaxation was not the cause for the low blood pressure He concluded that the blood had been drained into the dilated venules and capillaries and that the effect of this had been equivalent to exsanguination by hemorrhage.

Krogh endorsed Heubner s interpretation "These postmortem observations, together with the sudden fall of arterial pressure preceding death, show clearly that we have to do with a relaxation of the capillaries and venules to such an extent that only a fraction of the blood poured into them could return to the heart to keep up the circulation "

Capillary poisons include arsenicals mercurials and other salts of heavy metals. Hanzlik and Karsner studied the effects of various arsenical solutions given by injection Severe reactions resembling anaphylaxis resulted The postmortem examinations showed marked pulmonary and abdominal congestion and capillary hemorrhages. Our results justify the conclusion that the symptoms after the injection of arsenical compounds, whatever the form of arsenic, are of circulatory origin ' These authors obtained similar results from a large group of colloidal substances which produced anaphylactoid reactions when injected intravenously

It is known that intravenous injections of arsenicals for therapeutic purposes sometimes produce anaphylactoid or 'shock effects. This has been called the "nitritoid reaction because the flushing of the skin and the falling blood pressure resemble the circulatory effects of the nitrites The nausea, vomiting, edema, dyspnea perspiration unconsciousness and collapse may end in death as in shock from other causes. I have had occasion to perform necropsy examinations after two such fatalities In each instance the congestive hemorrhagic and edematous appearances of the viscera were those already described as the characteristic pathology of shock.

Mercuric poisoning may terminate fatally either by immediate effects or after a number of days as a result of renal damage When death occurs within two or three days, it often is preceded by manifestations of circulatory collapse McNider produced

acute poisoning by injecting mercuric chloride intravenously in dogs He stated that death within forty-eight hours was preceded by a condition of shock or collapse and that it was not due to renal insufficiency

Goldblatt recorded a progressive decline in blood pressure, accompanied by dyspnea, air hunger, increased respiratory rate and declining temperature as features in acute mercuric poisoning He described congestion and edema of the lungs and occasionally marked sub-pleural ecchymoses as pathologic findings in dogs These same features were observed by Harmon in human cases of acute poisoning followed by early death Others have made similar incidental observations but without comment on a relationship between the necropsy findings and the shock-like clinical manifestations

Landis demonstrated the injurious effects of mercuric chloride on endothelium by injecting a 1 to 10,000 solution into the blood This caused atony of the capillary walls and increased by sevenfold the permeability of the endothelium

Dr Crawford and I reported a case in which a man had swallowed about 175 gr of mercuric chloride with suicidal intent The clinician, Dr E Quinn Thornton, stated that the most pronounced signs were those of profound shock The patient neither vomited nor purged severely and there was little abdominal distress There was suppression of urine, the temperature declined and the blood pressure fell progressively in spite of fluids given intravenously From profound shock he sank into coma and died thirty-seven hours after taking the poison

The outstanding pathologic features were marked congestion and edema of the respiratory tract and of the abdominal viscera, the presence of blood-tinged effusions in all the serous cavities and capillary hemorrhages in the lungs, mucosæ and parenchymatous organs The usual effects of mercuric chloride were observed in the gastro-intestinal mucosa, the liver and the kidneys. The most significant feature was the condition of the lungs (Fig 19), whose combined weight was 1,830 gm after much blood and fluid had escaped as the lobes were sectioned and examined The microscopic appearance of the lung tissues (Fig 22) indicated extensive endothelial damage

We concluded that mercuric chloride, acting as a capillary poison, produces both the clinical and the pathologic features seen in shock originating in other ways

The substances which will produce anaphylactoid reactions are

numerous and are extremely varied in chemical composition It is significant that they include the entire group of Heidenhain's "lymphagogues." Peptone histamine bile, foreign sera, toxic proteins and products of protein cleavage, bacterial products, extracts of actinia, mussels crayfish and other marine animals snake venoms and numerous drugs and chemicals are included in this group These substances cause an increased flow of lymph by virtue of their injurious effects upon capillary endothelium (see Chart 1) They have in common no other physiologic or



FIG. 19 — Photograph of a lung from a person who died in shock from acute mercuric chloride poisoning A lung of normal color (right) was photographed for comparison.

chemical property Wells has emphasized that *the effects* of these, when injected intravenously are indistinguishable from anaphylaxis.

My associates and I have tested upon animals the action of many of the substances mentioned with results substantiating Wells observations. The animals became acutely ill hemoconcentration developed manifestations of acute shock were present and the animals died of circulatory failure The congestive hemorrhagic and edematous changes, seen in the tissues,

after death, were identical to those seen after anaphylaxis and after shock otherwise produced

Transfusion Reactions.—A characteristic circulatory disturbance is a frequent event after transfusion with incompatible blood The features of this vary somewhat, but discomfort, signs of collapse, weakness, perspiration, vomiting, chills, a sharp rise in temperature and a fall in blood pressure are the usual ones (Bordley) Suppressions of urine, albumin and hemoglobin in the urine, a progressive increase in the non-protein nitrogen, a low alkaline reserve, urticaria and purpura are prominent associated features Death from shock may occur in a few hours or days, otherwise marked deficiency of renal eliminations is the most striking feature of the delayed effects (see Extrarenal Uremia, Chapter XV)

The immediate reaction to transfusion with incompatible blood is called "allergic" or "anaphylactic" by many writers, this fact indicates the general character of the symptoms Changes seen at necropsy after early deaths are like those present in shock from other causes, these include pulmonary hyperemia, edema, purpuric spots in skin and mucosal surfaces, marked hepatic degeneration and focal necroses, renal degeneration, edema and hematogenous pigmentation

Most writers ascribe the systemic reaction to the effects of hemoglobin resulting from hemolysis of either the donor's or the recipient's corpuscles It has been shown (Phemister and Handy) that shock can be induced in dogs by withdrawing blood, traumatizing the corpuscles by shaking, then reinjecting the blood into the same dog Petroff and associates reported that injections of hemolysed blood produced the characteristic syndrome of shock in animals This was accompanied by a fall in arterial and venous blood pressure, decreased size of the heart, capillary paralysis and dilatation and stasis and by characteristic changes in the chemistry of the blood These features were like those produced by histamine Gesse's reports are in agreement with the findings of Petroff

The observations that shock or "collapse" frequently results from transfusion with incompatible blood has not been questioned The prevalent interpretation of the phenomena described is that products of hemolysis cause damage to endothelium, to hepatic cells and to renal epithelium The functional disturbances are explained as due chiefly to these injuries

Abdominal Emergencies.—Surgeons are familiar with the frequent occurrence of circulatory failure incident to grave abdominal conditions. Often the shock like character of these is recognized and there has been much discussion as to the cause of the manifestations An example of this is seen in high intestinal obstruction or strangulation There is no disagreement regarding the clinical manifestations of this nor that death results from circulatory failure

Cope observed that the most typical examples of secondary shock and collapse are seen in cases of intestinal obstruction Stone, Whipple and Bernheim made extensive studies on the effects of strangulation The contents of isolated or of strangulated loops, when injected into normal dogs produced violent illness and death like the effects of strangulation There were vomiting of fluid which contained bile, and diarrhea which was liquid and contained traces of blood Urination was suppressed, there was salivation the temperature declined and the blood pressure fell

Their description of the postmortem appearances is significant There was marked congestion of the lungs liver, kidneys and of the gastro-intestinal mucosæ. The lining of the small bowel was swollen and had a deep purple velvety appearance. The engorged villi were seen as tiny red specks The similarity of these features to those seen by Erlanger *et al* by Moon and others in experimental shock, is striking

Stone and associates concluded that toxic substances are formed in the obstructed loops and that the effects of these are to cause a fall in blood pressure, temperature disturbances, vomiting, diarrhea, disturbed renal function high non protein blood nitrogen delayed coagulation of the blood profound visceral congestion, collapse and death This interpretation has been substantiated by the work of Murphy and Brooks of Dragstedt and associates, of Hausler and Foster and of many others, but that interpretation is not held by all Some believe that the hemoconcentration and circulatory inefficiency result from the loss of chlorides and of fluid by vomiting

Morgan and I (288[9]) noted that the blood became concentrated rapidly after experimental strangulation of the small bowel in dogs. The dogs died of circulatory failure and the viscera showed the marked congestion edema and ecchymoses characteristic of shock When trypan blue was injected intravenously during life the viscera and the edema fluid became distinctly blue

in color This indicated increased endothelial permeability in extensive visceral areas

High intestinal obstruction is accompanied by persistent vomiting and is followed by peripheral circulatory failure in which hypochloremia, azotemia, hemoconcentration and other characteristics of shock are prominent It has been supposed that hypochloremia, resulting from loss of chlorides in the fluid vomited, was responsible for the entire syndrome This theory overlooks the fact that hypochloremia occurs in shock originating otherwise and that it is an effect, not a cause Haden and Orr produced intestinal obstruction in rabbits and observed that these developed hypochloremia and died with manifestations like those seen in other animals with obstruction Rabbits do not vomit, hence that explanation seems inadequate

We designed an experiment to determine whether continued vomiting, resulting from apomorphine, would cause concentration of the blood or other signs of shock Blood examinations were made and the dogs were weighed carefully prior to the experiment Food and water were withheld until the experiments were finished Repeated injections of apomorphine caused more voluminous vomiting than we have ever seen to result from experimental strangulation of the bowel In twenty-four hours the dogs had lost from 2 5 to 5 per cent of the body weight but showed no signs of circulatory disturbance Both the peripheral and the visceral tissues were shrunken and appeared dehydrated but *there was no detectable concentration of the blood* This experiment indicates that simple vomiting, even though prolonged and profuse, will cause neither hemoconcentration nor shock It appears that, if the mechanism of fluid balance is not deranged, a loss of fluid amounting to 5 per cent of the body weight will not alter the concentration of the blood nor impair the efficiency of the circulation

We concluded that the mechanism of death in high intestinal obstruction is not different from shock arising from other causes Subsequently Scudder and associates published extensive studies confirming this interpretation

Allchin (1907) described vividly the picture of shock which develops after the rupture or perforation of the appendix, stomach, intestine, gall bladder, or the bursting of an abscess into the peritoneal cavity The degree of shock may be so great that the patient dies within a few hours, befo[illegible] development of peritonitis occurs Th[illegible] rvatic [illegible] dantly confirmed in

more recent surgical literature. Cope noted that the immediate effect of such a catastrophe is primary shock (see p 256) which may merge into grave secondary shock, with or without an interval of time He listed the perforation of ulcers as an outstanding example of this. ' In cases of intensive peritonitis, secondary shock is seen in its worst form '

Clinical descriptions of acute pancreatitis emphasize shock as a prominent feature. "The onset is sudden like a thunderbolt from a clear sky The pain is overwhelming, accompanied by vomiting, rapid pulse, and signs of collapse more pronounced than in a perforating viscus" (Deaver) "Of the existence of shock in acute pancreatitis there is never the slightest doubt" (Moynihan) Finney and others substantiate these observations DeTakats and Mackenzie recorded hemoconcentration as a feature They suggested this as an indicator of the presence and of the degree of shock. I have made necropsy examination in 6 cases of acute pancreatitis and have reviewed the protocols of many others. In each instance both the clinical features and the necropsy findings were those characteristic of shock.

The evidence justifies the conclusion that circulatory failure of the shock type is a prominent feature in a wide variety of abdominal catastrophes

The occurrence of shock after physical trauma, extensive surgical operations or severe burns is an event easily recognized for in such instances the onset is rapid and the signs are usually unmistakable The clinical manifestations and the physiologic disorders are those described in preceding chapters When that syndrome develops in a previously healthy person as a result of physical trauma, surgery or burns its onset and ominous progress seldom escape recognition But when the same type of circulatory deficiency develops gradually in the course of some preëxisting disease, its presence may be unrecognized or overlooked If detected, it is often misinterpreted as evidence of cardiac failure or of vasomotor collapse

Metabolic Intoxications.—Death by circulatory failure having the essential features of shock as defined occurs occasionally in conditions of grave metabolic disorders such as are seen in toxic jaundice or icterus gravis, in diabetic acidosis and in toxemia as a complication of pregnancy Atchley's discussion of 'medical shock' included metabolic intoxications among the causes Eppinger emphasized icterus gravis and catarrhal jaundice as

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Obstetric Shock.—The development of circulatory collapse in the course of pregnancy or labor has been recorded by many writers. As in shock due to trauma, hemorrhage may be an important contributory factor That loss of blood is not the primary cause is indicated by the occurrence of collapse when little or no blood has been lost, by the associated hemoconcentration, by the conditions found in the viscera at necropsy and by the fact that the results of massive hemorrhages may be counteracted more effectively by infusions of fluids or by transfusion, while in shock these may fail to restore circulatory efficiency

Cox (1853) described an instance in which collapse accompanied by insignificant hemorrhage occurred in a young healthy primipara Bailey noted that the rapid decline in blood pressure seen in collapse associated with eclampsia, resembled the effect of veratrin Driscoll reported that the most serious type of shock may occur in "nephritic toxemia" during pregnancy He noted also the contributory effects of anesthesia when operative procedures were undertaken in such cases

Adair, Hunt and Arnell analyzed the "vascular collapse in toxemias of pregnancy" seen in 1018 such cases. A marked fall in blood pressure, prior to delivery and unaccompanied by hemorrhage, was recorded in many instances McIllroy concluded that shock associated with the puerperal state is due to a condition of toxemia. Adair and Stieglitz noted that the clinical feature in such cases resembled those of anaphylaxis. They recognized this as a grave complication of pregnancy

De Lee confirmed the observations just cited and noted hemoconcentration as indicated by increased numbers of erythrocytes In one case a count of 9 000,000 was recorded He stated that syncope during eclampsia or sepsis is attended by acute pulmonary edema and that the condition resembles anaphylaxis The necropsy findings in fatal cases were significant Congestion, edema and petechial hemorrhages were found in the brain The liver showed degeneration and contained areas of hemorrhagic necroses. Parenchymatous and fatty degeneration found in the kidneys were attributed to the toxemia. "We believe that the nephritis (in eclampsia) is only a part of a general disturbance affecting all the capillaries and body tissues The lungs were hyperemic and edematous and frequently there were petechial hemorrhages in the pleuræ and epicardium Broncho-pneumonia was a terminal complication in many instances (see Chapter XIV)

Most of the pathologic studies on eclampsia have emphasized

illustrating the development of shock in clinical cases He recorded hemoconcentration as a characteristic feature

I have reported 2 cases in which severe intoxication associated with acute hepatic necrosis presented the clinical features of shock In one of these, the concentration of the blood reached 40 per cent while the blood pressure was at its highest recorded point The blood pressure declined steadily during the twenty-four hours preceding death Postmortem examination revealed extensive hepatic necrosis and the circulatory features which are characteristic of shock

My associates and I have produced shock in dogs by implanting liver substance in the peritoneal cavity and by injecting bile or sodium glycocholate intraperitoneally or intravenously The manifestations and postmortem findings were indistinguishable from those of shock otherwise produced These experiments do not bear upon the causation of icterus gravis or of catarrhal jaundice, but they indicate that the absorption of bile or of damaged liver substance may produce circulatory effects resulting in shock

Metabolic intoxication is a prominent feature in advanced stages of diabetes Ketone bodies, diacetic acid and β-oxybutyric acid are known products resulting from the imperfect oxydation of fats "The metabolic fire may be said to smoke with these poisonous products of incomplete fat combustion" (Boyd) In Atchley's experience "the acidosis of diabetes affords the most clean cut example of medical shock" and most deaths in diabetic coma are due to shock "How far shock may be responsible for the symptoms and fatalities in diabetic acidosis is still uncertain, but its part probably has been greatly underestimated" (Peters) Schecter, Wiesel and Cohn recently cited previous observations on the shock syndrome in diabetic acidosis They reported 8 cases in which low blood pressure, high hemoglobin and hematocrit readings, and reduced volume flow of blood were manifestations of peripheral circulatory failure They believed this syndrome resulted from some histo-toxic factor combined with the effects of anoxia

Warren has described visceral congestion, edema and ecchymoses in mucous and serous surfaces as the usual necropsy findings after death from diabetes I have made the same observations at postmortem in such cases Apparently the intoxication of diabetes affects the circulation in much the same manner as do other agents which cause endothelial damage

Infections.—A condition of circulatory collapse often develops in severe infections. This is independent of the species of the *infecting agent*, but appears to depend on the severity of the individual case. "There is no doubt that the cleavage products produced from protein by the action of ferments or bacteria can produce a condition in many ways resembling the secondary shock described by military surgeons The recognition of this factor brings secondary shock into relation with the state of collapse produced by severe bacterial toxemia (Dale) Atchley described this phenomenon as an instance of ' medical shock.

"Doubtless you will all recall in your own experiences with severe infectious diseases particularly pneumonia and typhoid fever patients who have presented the picture of falling blood pressure, rapid pulse and collapse Certainly in many instances this serious complication is a manifestation of shock and probably results from an increase in the vascular bed due to capillary damage. Confusion of this state with cardiac failure will result in misdirected and possibly harmful therapy There is no doubt that the importance of the state of shock particularly as it occurs in the field of internal medicine has not received its just and proper emphasis

He noted the picture of shock presented in fatal cases of influenza, also in the systemic reaction to an overdose of pneumococcal vaccine Warfield confirmed the previous observations and attributed the circulatory deficiency to the effects of histamine like substances on the capillaries he recognized low blood volume and *hemoconcentration as characteristic features*.

MacCallum observed that severely infected patients may die with symptoms like those of surgical shock and gave diphtheritic intoxication as a characteristic example Harding analyzed over 800 cases of diphtheria and stated that the toxemic stage closely resembles wound shock or the effects of severe hemorrhage She recorded hemoconcentration and edema of the tissues as prominent features in such cases and attributed these to increased permeability of the capillary endothelium Dieckhoff made estimations of blood volume in children severely ill of diphtheria and showing signs of collapse The total blood volume was decreased by about 50 per cent and increased concentration of corpuscles was shown by hematocrit.

The injection of diphtheritic toxin intravenously will produce anaphylactoid manifestations and death Ewing reported circulatory collapse accompanied by hemoconcentration developing in animals after injections of toxins derived from typhoid bacilli

renal abnormalities and have failed to record the appearance seen elsewhere When the conditions in other viscera have been described, they conform closely to the pathology of shock Lubarsch reviewed the pathologic finding in 69 reported cases and in 16 necropsies of his own Regularly the lungs were deeply congested, edematous and contained ecchymoses What was described as "a hemorrhagic broncho-pneumonia" was present in a majority of the cases The bacterial flora as shown by direct microscopy and by cultures, was mixed and indicated that the pneumonia was a secondary process, not due to any specific type of organism Similar findings have been reported by Francesco, Bell and others This type of pneumonia, occurring as a terminal event in sublethal shock, is discussed in Chapter XIV

In some cases Sheehan found ecchymoses beneath the epicardium, in the peritoneum and in the ovaries and lungs He did not attempt to draw distinctions between true shock uncomplicated by hemorrhage, and circulatory failure in which loss of blood was the chief factor Hence his findings cannot be analyzed accurately

Hansen discussed circulatory collapse incident to pregnancy and labor, under 5 headings or groups according to the chief cause *Anemia* due chiefly to hemorrhage, *nervous collapse*, resulting from vasomotor reflexes, *toxic collapse* was assigned to the action of some biochemical agent and was exemplified by the intoxication of eclampsia He regarded one form of this which he designated "eclampsia without convulsions" as especially grave because it does not yield to treatment and usually terminates in death by circulatory failure

Recently Matthews summarized the subject of obstetric shock and emphasized hemoconcentration as a means for its recognition and its differentiation from hemorrhage A survey of reports indicates that shock may occur as a complication of pregnancy under two principal conditions as a result of toxemia or as a complication of prolonged or difficult labor In the latter condition, hemorrhage is frequently a contributory factor of major or minor importance I have made necropsy examinations in each of these types of obstetrical shock and have found the visceral changes characteristic of shock in each When hemorrhage has been a major factor the viscera are dry and ischemic

Both the clinical and the pathologic evidence indicates that circulatory failure of the shock type may occur as a complication of pregnancy or of the puerperal state

Infections.—A condition of circulatory collapse often develops in severe infections. This is independent of the species of the infecting agent, but appears to depend on the severity of the individual case "There is no doubt that the cleavage products produced from protein by the action of ferments or bacteria can produce a condition in many ways resembling the secondary shock described by military surgeons. The recognition of this factor brings secondary shock into relation with the state of collapse produced by severe bacterial toxemia" (Dale) Atchley described this phenomenon as an instance of "medical shock"

> Doubtless you will all recall in your own experiences with severe infectious diseases, particularly pneumonia and typhoid fever patients who have presented the picture of falling blood pressure, rapid pulse and collapse Certainly in many instances this serious complication is a manifestation of shock and probably results from an increase in the vascular bed due to capillary damage. Confusion of this state with cardiac failure will result in misdirected and possibly harmful therapy There is no doubt that the importance of the state of shock particularly as it occurs in the field of internal medicine has not received its just and proper emphasis."

He noted the picture of shock presented in fatal cases of influenza also in the systemic reaction to an overdose of pneumococcal vaccine. Warfield confirmed the previous observations and attributed the circulatory deficiency to the effects of histamine like substances on the capillaries he recognized low blood volume and hemoconcentration as characteristic features

MacCallum observed that severely infected patients may die with symptoms like those of surgical shock, and gave diphtheritic intoxication as a characteristic example Harding analyzed over 800 cases of diphtheria and stated that the toxemic stage closely resembles wound shock or the effects of severe hemorrhage She recorded hemoconcentration and edema of the tissues as prominent features in such cases and attributed these to increased permeability of the capillary endothelium Dieckhoff made estimations of blood volume in children severely ill of diphtheria and showing signs of collapse The total blood volume was decreased by about 50 per cent and increased concentration of corpuscles was shown by hematocrit.

The injection of diphtheritic toxin intravenously will produce anaphylactoid manifestations and death Ewing reported circulatory collapse accompanied by hemoconcentration developing in animals after injections of toxins derived from typhoid bacilli

I have produced these effects in dogs by injecting bacteria-free filtrates from cultures of enterococci and streptococci Many such results have been recorded by others

Rapidly fatal cases of influenza, dying within twenty-four to seventy-two hours, manifested circulatory failure which the clinicians termed collapse or shock My curiosity concerning this phenomenon was first excited by the fact that erythrocytic counts in such cases ranged between 6,000,000 and 8,000,000 At that time I could find no satisfactory explanation for this acute erythrocytosis Underhill and Ringer found hemoglobin values ranging from 110 to 140 per cent in severe cases Death resulted in each such instance There was no instance of hemoconcentration followed by recovery These rapidly fatal cases did not die of penumonia The postmortem findings were exactly similar to those found after death from severe burns of the skin or those resulting from acute poisoning as with mercuric chloride

Eppinger and Schurmeyer stated that the capillaries appear to be injured in varying degrees in all acute febrile diseases They observed that in most instances, shock does not develop early but at the height of the illness or during convalescence, it comes on not suddenly but gradually and insidiously, usually leading to immediate death The "false crisis," seen in typhoid fever or pneumonia, was explained as due to the onset of shock Fishberg stated that circulatory failure in acute infectious diseases is usually peripheral rather than cardiac in origin, the clinical picture is fundamentally the same as in traumatic shock In such cases the symptomatology was such as to leave no doubt of the peripheral origin of the circulatory failure "Shock is one of the developments most to be feared in pneumonia Except for patients with antecedent heart disease, whose greatest danger is heart failure, death in pneumonia is generally ushered in by peripheral circulatory collapse The picture is the classical one in shock "

Stewart called attention to the syndrome of postoperative shock caused by fulminating hemolytic streptococcal infection of the wound He reported four instances of this condition There was an interim of twenty-four hours after the onset of shock before the presence of wound infection was suspected or shown

The products of bacterial growth in contaminated wounds contribute in an immeasurable degree to the development of shock This statement applies to saprophytic as well as pathogenic organisms Devitalized tissues provide an optimum medium for bacterial growth, products of which produce systemic

effects when absorbed. The early débridement of such wounds reduces this factor effectively

Death by peripheral circulatory failure occurs also in typhoid fever, typhus, yellow fever, plague, puerperal sepsis, scarlet fever erysipelas and in other severe acute infections Circulatory failure in these conditions is often assigned erroneously to cardiac weakness by internists and surgeons. Likewise pathologists often make an unwarranted assumption in applying the term *acute passive congestion* to engorged edematous and ecchymotic appearances in the viscera except when there are demonstrable primary pathologic changes in the heart. In the absence of cardiac pathology, many instances of so-called *congestive heart failure* may be found to be *peripheral* rather than *cardiac* in origin

Summary —It appears that the circulatory failure in anaphylaxis results from the effect of the foreign protein upon the sensitized capillary endothelium When given intravenously, this effect is almost instantaneous, the immediate capillary atony and abnormal permeability of the endothelium account for the sudden disturbance of the circulation When death does not follow immediately, the clinical signs and the chemical changes in the blood are the same as in shock from other causes. The validity of this interpretation is substantiated by the tissue changes seen at necropsy

Many chemicals and poisonous substances derived from plants, animals and bacteria, produce anaphylactoid or "nitritoid" reactions by virtue of their effects upon endothelium This action accounts for the similarity of the signs and symptoms to those of anaphylaxis

The reaction from transfusion with incompatible blood is similar to that of anaphylaxis and appears to originate from the effects of hemolysed erythrocytes upon endothelium

Abdominal catastrophes such as intestinal obstruction, strangulation perforations, mesenteric thrombosis, pancreatitis, and acute general peritonitis, regularly present the syndrome of shock Vomiting is a feature in these as in other instances described However loss of chlorides in the fluid vomited is not an adequate explanation for the associated manifestations Intoxication with products absorbed from damaged mucosæ and other tissues, from intestinal contents from bacterial contamination and infection, appears as a major factor in disturbing the systemic circulation

So-called metabolic intoxications often lead to peripheral circulatory failure These include toxic jaundice or icterus gravis diabetes and the toxemias of pregnancy The nature of the

intoxicating agents has not been shown, but the character of the symptoms and the changes found at necropsy leave no doubt as to the relation between these and the syndrome of shock Degeneration and necrosis of liver is a prominent feature in this group, substances produced by autolysis of liver may be an important contributory factor, such substances are effective in producing shock experimentally

Infections of unusual severity will produce all the manifestations and disturbances which accompany shock Dale recognized this fact and included products of bacterial growth and of infection, among the agents which have a histamine-like action

The one factor common to all these conditions is endothelial permeability with consequent disturbance of the circulation and of fluid balance In anaphylactic and anaphylactoid states, the endothelium appears to be injured directly by the agent used In the other instances it appears that products of proteolysis, metabolic "toxins" and substances resulting from bacterial growth and infection, affect endothelium with similar results

CHAPTER XIV

SUBLETHAL SHOCK

SHOCK is a circulatory deficiency which occurs in varying degrees and with varying rapidity This statement may seem to emphasize the obvious, but the fact itself is so important as to justify the emphasis. Maximal degrees of shock lead rapidly to death minimal degrees are followed by recovery The effects of intermediate or sublethal degrees of shock have not received adequate consideration as complications in surgical and medical conditions The complications which develop when shock persists for several days, are discussed in this and in the subsequent chapter

EDEMA

The term *edema* is applied to an abnormal accumulation of fluid in the cells and spaces of living tissues. Understanding of all the forces which may contribute to this condition is not complete It is known, however, that three major factors contribute to the development of edema Elevation of capillary blood pressure, variations in osmotic pressure between the plasma and the tissue fluids, and increased permeability of the capillary endothelium Space is lacking for a consideration of the first two of these factors but evidence concerning increased endothelial permeability will be summarized

Researches on capillary physiology have shown that any type of injury to endothelium impairs its normal impermeability to protein and to other colloids Landis found that capillaries damaged experimentally by various agents became 7 times more permeable than normal "In view of this seven fold increase in permeability the rapidity with which shock or inflammatory edema develops does not seem so extraordinary He showed that severe capillary damage produced prompt stasis of the circulation and little edema, while lesser degrees of damage produced marked edema. This observation coincides accurately with the experience of my associates and myself in the experimental production of shock by various means.

When shock developed rapidly and death occurred early there was little visible edema but very marked stasis engorgement and capillary hemorrhages were present Such results followed the

intravenous injection of histamine, peptone, snake venom, various tissue extracts and foreign protein in sensitized animals When death occurred at longer intervals the edema was progressively more marked The implantation of small amounts of muscle pulp or of other tissue substance in the peritoneal cavity often caused death after twenty-four hours or longer Death after extensive trauma, surgical procedures, burns, or from shock originating otherwise in man seldom occurs in less than twenty-four hours In such experimental and clinical conditions there is marked edema, particularly of the lungs and mucosæ

Eppinger gave detailed consideration to circulatory collapse occurring in various clinical conditions These included burns, food poisoning, metabolic intoxications, severe infections and the effects of veronal and other poisons He found hemoconcentration in all cases of shock, regardless of the condition causing it, and attributed it to increased permeability of the capillary membranes He found albuminous fluid in the intercellular spaces of the tissues in each of the conditions mentioned This fluid had a high protein content, approaching closely that of the blood plasma The increased permeability of the endothelium, which resulted in leakage of plasma and in hemoconcentration, was regarded as of such primary importance that it constituted the title of his monograph "Die serose Entzundung"

Pulmonary edema occurs clinically and is seen at necropsy with great frequency Its presence associated with subacute nephritis, cardiac decompensation, starvation or dietary deficiencies, is not difficult to interpret Another type of pulmonary edema occurs in cases of severe acute infection, intoxications, serum disease, poisoning with veronal, emetine and with other drugs, also after burns, extensive trauma, and prolonged or complicated surgical procedures In such cases the fluid has a high specific gravity and a protein content closely approximating that of the blood plasma

There have been only a few reports on the experimental production of this type of pulmonary edema Grossman found that intravenous injections of muscarin caused a fall in blood pressure followed by death. The lungs in dogs so treated were markedly edematous Lowit confirmed these observations Miller and Matthews injected an aqueous solution of iodine intravenously into animals This produced marked edema of the lungs which they attributed to vascular injury

Auer and Gates, Schmidt and others found that injections of

adrenalin in large doses produced disturbances of the circulation and, in severe cases, death There were marked pulmonary edema and numerous hemorrhages in the lungs in these animals. Bainbridge and Trevan, Erlanger *et al*, and others produced similar effects. The mechanism by which adrenalin causes shock has been discussed in a previous chapter

Manwaring and his associates perfused isolated organs of dogs sensitized to horse serum, with fluid containing small amounts of horse protein Such experiments resulted in marked edema of the lungs and of the intestines Similar perfusion in non sensitized dogs produced no such effect They regarded these results as indicating that in anaphylaxis the capillary walls are rendered abnormally permeable

Underhill and others have shown that marked edema of the lungs results from the inhalation of various irritating or poisonous gases. This was observed as a most distressing feature in those gassed with chlorine or phosgene during World War I Death in such cases was attributed directly to the pulmonary edema Underhill noted marked hemoconcentration in such cases and in dogs after inhalations of similar gases. This was explained as due to the leakage of the blood plasma into the alveoli of the lungs leaving the blood more concentrated

Lambert and Gremels produced edema by perfusing the vessels of "heart lung preparations" with defibrinated blood which had been stored in refrigeration Such defibrinated blood appeared to be very toxic to such organs. Edema was produced also by adding minute quantities of poisons such as silver nitrate to the perfusion fluid They recognized abnormal permeability of the capillaries as the cause for the escape of fluid from the blood and saw in these experiments a possible explanation of the pathogenesis of pulmonary edema in man

These observations suggested to us that pulmonary edema might be produced experimentally by inducing shock of gradual development or in degrees not immediately fatal Accordingly sublethal degrees of shock were produced by various means and the effects noted

Fresh muscle pulp as described in Chapter XI, was implanted intraperitoneally in doses ranging from 2 5 to 3.5 gm per kilogram These doses were smaller than those which caused rapidly fatal effects. The dogs became ill and hemoconcentration developed as in the previous experiments. Death occurred at intervals ranging from thirty-six hours to four days. The lungs were found

engorged and much above normal weight Blood-tinged frothy fluid escaped in quantities when pressure was applied after sectioning This fluid had a high protein content and the specific gravity was only slightly below that of the blood plasma In

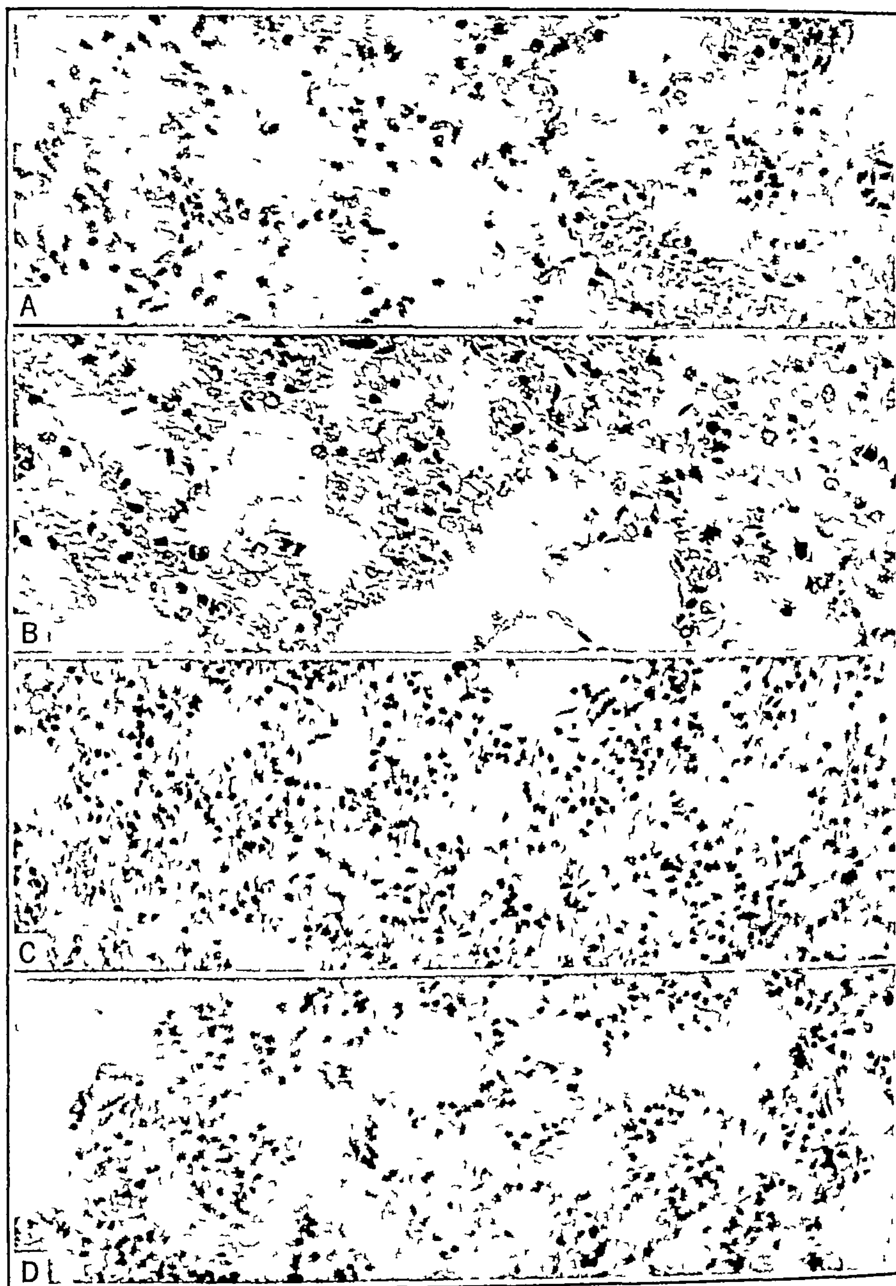


FIG 20 —Experimental pulmonary edema *A*, Induced by subcutaneous injections of histamine *B*, Induced by scalding of the skin *C*, Induced by tissue autolysis *in vivo* *D*, Induced by intestinal strangulation

some cases there was blood tinged fluid in the pericardial and pleural cavities In other particulars the necropsy findings were like those already recorded after experimental shock (Fig 19)

Exactly similar results were obtained when shock with delayed death was produced by other means These included burns intestinal obstruction, barbital given by mouth, bile, cholic salts peptone, foreign proteins and histamine given by injection In each instance, hemoconcentration was an antemortem feature and the specific gravity of the edema fluid was almost equal to that of the blood plasma. Edema of this type results from increased endothelial permeability Apparently, various agents and conditions which cause injury to endothelium will produce edema provided the dosage given is not sufficient to cause imme diate death

The mechanism of origin of this type of pulmonary edema is integral with that of shock.

TERMINAL PNEUMONIA

Each of the various conditions in which sublethal shock occurs are predisposed to develop secondary pneumonia as a terminal complication. Lungs in which the circulation is sluggish and in which the spaces are filled with albuminous fluid—edema—present conditions ideal for the development of pneumonia Human respiratory passages harbor various pathogenic organisms, and the edema fluid provides an excellent culture medium for their growth Systemic resistance may have been lowered by disease injury or intoxication, and pulmonary resistance is impaired by the circulatory inefficiency *Under such conditions the development of pneumonia is almost inevitable* The mechanism of its origin is identical with that of pneumonia in pulmonary passive congestion incident to cardiac decompensation. The difference lies in the mode of origin of the congestion and edema.

Morphologic Features.—In such pneumonia the lungs present varying degrees of diffuse widespread congestion edema and irregular patchy consolidation Due to the effect of gravity these findings are most marked in the dependent portions. Grossly such lungs are heavy wet and of increased density The con solidated areas are ill defined by palpation, merging imperceptibly with adjacent areas of congestion and edema. The lungs have a deep reddish purple color When they are sectioned frothy sero-sanguineous fluid escapes freely and the bronchial mucosa is swollen, edematous and cyanotic

The areas of consolidation vary greatly in size, distributio number, depending on the degree of the congestive proce the time elapsing before death Occasionally the areas b confluent and extensive but then the condition does not res lobar pneumonia The consolidation, even when compl not firm but rather soft and edematous, increasingly so t the anterior portions Also the color is less uniform and pr a mottling of darker red and lighter grayish red patches N does this condition resemble true broncho-pneumonia for i not arise from the bronchi nor does its distribution confo all to that of the bronchial branches

Microscopic examination shows marked engorgement c capillaries and venules, and albuminous fluid filling the a The fluid contains varying numbers of leukocytes, chiefly morphonuclear in type The mononuclear forms, howeve more numerous than in primary pneumonias The leuk distribution is not uniform, some areas contain only a few, contain many, and in others they are densely packed The ex may contain red cells from capillary hemorrhages and fron pedesis and sometimes hematogenous pigmentation is prom The outstanding microscopic features are the congestion evident stasis of blood in the minute vessels and the re absence of fibrin, even where consolidation is most m (Fig 22)

The bacteriologic findings are inconstant No one orga or type of organisms provides the infectious factor As in "l static pneumonia" and in that of cardiac decompensation bacterial flora is mixed and various Several organisms are us present in cultures from consolidated areas Pneumo streptococci, staphylococci and Micrococcus catarrhalis dominate, but various bacilli may be cultivated also Wha bacterial forms are present in the person's respiratory tract determine largely those recovered by culture from the pneun areas This is essentially a mixed infection

Postoperative Pneumonia.—Surgeons are keenly aware o danger of pneumonia after extensive surgical procedures has been attributed to such factors as the aspiration of sa the irritating effect of ether on the respiratory mucosa or loss of body heat during or after the operation But I have no discussion in which the development of a sublethal degr shock was suggested as a possible factor That such pneum is not due to aspiration of saliva or to bronchial irritation, is sh

by its distribution It does not arise about bronchi nor does it conform in any particular to their distribution

Very frequently I have found secondary pneumonia in hyperemic edematous lungs when death has occurred a few days after extensive surgical procedures. When erythrocytic counts were made after the operations they showed hemoconcentration which indicated that the mechanism of shock was operative It seems probable in such cases that a subclinical degree of shock has occurred, incident to the operation, and that this was the precursor for terminal pneumonia.



FIG. 21 —Incipient pneumonia after poisoning with mercuric chloride. Leukocytic infiltration is beginning in hyperemic, edematous lung tissue.

Pneumonia After Burns.—It is well known that extensive burns result in death through shock The pathologic features seen at necropsy are of the same type as seen in shock from other causes. One of 3 results may be expected after severe burns death through shock within forty-eight hours subsequently death from pneumonia, or recovery An accident in which 3 men were burned and brought to the hospital at the same time furnishes an instance of these results Shock was a pronounced feature in each case as shown by clinical signs and by hemoconcentration The blood of the man most severely burned contained 8 350 000 red cells per cubic millimeter a few hours after the accident. He died within forty-eight hours and the necropsy showed the visceral congestion edema and ecchymoses usually found after death from burns.

Another of the victims lived seven days During this time the erythrocytic counts fluctuated between 4,600,000 and 6,000,000 Marked bilateral pneumonia in congested edematous lungs was shown postmortem This had all the features described in the section on morphologic characteristics

The man whose burns were least extensive lived The concentration of his blood decreased gradually as his condition progressed toward recovery

These cases are cited as illustrative of the usual results of extensive superficial burns and of the occurrence of pneumonia of the type under consideration We have found terminal pneumonia also in animals that lived six or eight days after experimental burns

Pneumonia After Anesthetic and Hypnotic Drugs.—Several therapeutic agents of this class tend to produce circulatory failure like that of shock if given in large doses The barbiturates used as sedatives and as anesthetics for man and for animals under experimentation furnish an excellent example of this action It is well known that some of these will produce manifestations like those of shock

Seevers and Tatum recorded marked visceral hyperemia at postmortem examination after prolonged use of barbital in small doses (0 1 gm per kilogram) in dogs There were subendocardial hemorrhages, the lungs were intensely congested, and extravasated blood was seen in the alveoli and bronchi There were intense congestion and capillary hemorrhages in the gastro-intestinal mucosa, and the liver, kidneys, adrenals and meninges were hyperemic These same features are recorded as the characteristic appearances after death from overdoses of veronal and of other barbiturates The similarity of these circulatory effects to those of other agents injurious to capillaries, needs no emphasis

I have found these same congestive, hemorrhagic and edematous features after profound narcosis obtained with compounds of barbital Dr Morgan and I (288[6]) reported on the effects of sodium phenobarbital given by mouth in the production of experimental pulmonary edema This caused hemoconcentration and death by circulatory failure in dogs The visceral appearances were the same as after shock otherwise produced Pulmonary hyperemia and edema were prominent Pneumonia of the type discussed developed in 2 dogs in which deep narcosis was continued several days

There have been reports of pneumonia and other untoward effects from deep anesthesia obtained with barbiturates and similar drugs. I have described an instance in which an overdose



FIG. 22.—*A* photomicrograph of the margin of a pneumonic area. Death occurred four days after prostatectomy the wound being noninfected. Varying degrees of leukocytic infiltration in a congested edematous lung are shown. Magnification about × 50 *B* a higher magnification (about × 250) of an area from the same section as *A* Engorgement of minute vessels and irregular leukocytic infiltration are shown. (Moon courtesy of Arch Path.)

of sedormid produced profound narcosis and death by circulatory failure The pathologic features of shock were present in characteristic pattern Pneumonia was already developing in the

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condition of the lungs corresponds to the morphologic description of secondary pneumonia given in a preceding section

Bacteriologic reports on influenzal pneumonia made in 1918–1919 from laboratories in various parts of the world showed no uniformity of results. The fact that various organisms were cultivated and that mixed cultures were obtained in most cases led to the belief that the pneumonia was a secondary infection with whatever organisms predominated in the patient's respiratory tract at the time It was concluded by some that the primary infectious agent of influenza was not cultivable by the usual methods and had not yet been demonstrated Subsequent developments have supported these views.

Both the clinical signs of shock in severe influenza and in other fulminating infections, the finding of pulmonary congestion and edema after death in such cases and the development of hemorrhagic edematous pneumonia when death has been somewhat delayed indicate that terminal pneumonia in severe infections originates by the same mechanism as that of sublethal shock

Terminal Pneumonia in Other Conditions.—The occurrence of shock during eclampsia, diabetes intestinal obstruction icterus gravis, pancreatitis, severe infections poisoning and other conditions was discussed in the preceding chapter Medical literature contains many references to pneumonia as a terminal event or as a postmortem observation in these and similar conditions Only a few such reports will be cited.

Lubarsch noted the same visceral appearances after death from eclampsia as my co-workers and I have found regularly in shock He reported also that in the majority of such cases "hemorrhagic broncho-pneumonia was present The involved areas contained various bacteria, indicating that the pneumonia was due to secondary infection This type of pneumonia was present in a case of eclampsia which I have reported The lungs in this instance were indistinguishable from those in cases of influenzal pneumonia.

Brown and his associates reported from the Mayo Clinic 11 cases of chronic duodenal obstruction in which a syndrome was presented which they termed duodenal toxemia. Prominent clinical features of this were vomiting of serous bile-staining fluid, evidences of dehydration high hemoglobin content of the blood, low blood pressure asthenia and evidences of shock associated with low renal function The authors emphasized a form of toxic

nephritis as a complication, but the case histories serve also to portray the gradual development of sublethal shock Six of the patients died and necropsy showed nephrosis or toxic nephritis in each Evidence of disturbed renal function in the other five patients disappeared as they recovered "Broncho-pneumonia" was found at necropsy in each of the 6 patients who died This was described as patchy in some and as coalescing in others

Finkelstein and Jacobi reviewed the clinical and postmortem features of poisoning with iodine Shock was recognized as a clinical feature in 11 of 18 cases Marked pulmonary hyperemia, frothy serosanguineous fluid in the bronchi and alveolar spaces and edema of the mucosa were described The pleuræ were reddened and dull, and the gastro-intestinal mucosa was also congested and edematous The authors emphasized the frequency of such pulmonary involvement and noted the tendency to pneumonia The same type of widespread visceral congestion and edema occurs in instances of early death from mercuric chloride poisoning The finest example of incipient pneumonia that I have seen was in such a case of death from shock, which Crawford and I reported (Fig 21) The lungs were heavy, wet and bloody, exactly like those seen in cases of severest influenza The beginning of leukocytic infiltration was easily recognized in several areas although death occurred only thirty-seven hours after the poison was taken

I have found this type of pneumonia in examinations made after deaths from typhoid fever, peritonitis, erysipelas, chronic intestinal obstruction, perforation of a gastric ulcer, icterus gravis and various so-called toxemias In material from 100 unselected autopsies on adults, this type of terminal pneumonia was found in 16 instances Cases were not included in which pulmonary congestion and edema occurred from cardiac or renal causes Eight cases occurred after surgical procedures and 8 cases after the following conditions respectively acute hemorrhagic pancreatitis, ulcerative colitis, drug poisoning (sedormid), obstructive jaundice, eclampsia, extensive burns of the skin, diabetic acidosis and peritonitis Subsequent experience indicates that the percentage occurrence of terminal pneumonia is above rather than below that shown in this group of 100

Pneumonia was found at postmortem examination in many of our experiments on sublethal shock with delayed death This occurred in both dogs and rabbits and followed the implantation of small quantities of liver or muscle pulp in the peritoneal cavity,

burns, barbital narcosis, injection of bile and other procedures by which sublethal shock was produced

Summary —Evidence presented in preceding chapters indicates that the shock syndrome occurs in a wide variety of clinical disorders. This generalization is supported by the recorded observations of physicians in various fields of medical practice It is equally evident that the syndrome of shock develops in varying degrees. Maximal degrees rapidly lead to death from circulatory failure, minimal degrees may be followed by recovery Intermediate degrees, not immediately fatal tend to produce clinical and pathologic changes not recognized hitherto as related to shock

One of these is the development of visceral edema, particularly in the lungs. This may occur rapidly as in serum sickness severe burns or influenza. The development of pulmonary edema may be gradual and insidious after injuries operations intestinal obstruction, burns of lesser extent and during severe infections and intoxications.

A type of hemorrhagic edematous pneumonia is a very common sequel in shock of sublethal degree Congestion, stasis and edema are the factors initiating this form of terminal pneumonia. The infectious factor is supplied by whatever pathogenic bacteria are present in the respiratory tract of the individual.

When the circulation is impaired and the pulmonary spaces are filled with albuminous fluid the development of terminal pneumonia is almost inevitable unless death or recovery occurs promptly

CHAPTER XV

EXTRARENAL UREMIA

IMPAIRMENT of renal function occurs whenever a severe degree of shock develops The presence of oliguria, albuminuria and the associated increase in the non-protein nitrogen of the blood were discussed in Chapter III The importance of this complication is such that it was mentioned as an item in the revised definition for this type of circulatory deficiency (p 44)

When shock of sublethal degree persists for several days, its presence is not always recognized but the renal deficiency becomes a prominent clinical feature

OCCURRENCE

The term *extrarenal uremia* implies the retention of nitrogenous wastes, accompanied by oliguria and other evidences of renal dysfunction, independent of organic renal disease Bell states "The kidneys may be found entirely normal or the structural changes may afford only an inadequate explanation of the uremia In the great majority of cases of extrarenal uremia the suppression of urine and subsequent uremia is due to dehydration The blood resists concentration and no fluid is available for the formation of urine Nitrogenous products accumulate in the blood because they are not excreted and also *because of an increased destruction of protein*" (italics mine)

Bell reported case histories and necropsy findings illustrating this syndrome in various clinical conditions These occurred after major surgical procedures, fracture followed by infection, poisoning with phenobarbital, icterus gravis, alcoholism, persistent vomiting of undetermined cause, diabetic coma (3 cases), pancreatitis (2 cases), peritonitis, paralytic ileus, streptococcal cellulitis, suppurative cholangitis, and transfusion with incompatible blood (2 cases) In 1 of the latter he had no data concerning the immediate reaction to the transfusion, in the other, shock was obvious "She recovered from shock but in the next twenty-four hours passed only 50 cc of urine This had a specific gravity of 1 035, a 4 plus albumin and large amounts of hemoglobin " The patient became jaundiced, the blood urea rose to 144 and the creatinin to 9 9 mg per cent, pulmonary edema developed and

the patient died The necropsy revealed marked pulmonary edema, 500 cc. of clear ascites in the peritoneal cavity and large pale kidneys. Microscopically these showed dilated tubules interstitial edema, tubular casts consisting of hemoglobin and erythrocytes, but no necrosis nor organic renal disease

Lambret and Driessens studied the physiologic disturbances which accompany shock as an aftermath of extensive surgical procedures. They discussed it as a complex tissue fluid syndrome characterized by reduced blood volume, acidosis hypochloremia hyperglycemia and hyperazotemia They emphasized that the retention of urea occurred in variable degrees often reaching five times that of normal blood They cited instances in which the blood urea ranged between 250 and 330 mg per cent In mild cases, this returned to a normal level in twenty four to thirty six hours, in more severe cases, it remained abnormally high for several days and in some it progressed to such a degree as to dominate the clinical picture

Helwig and Schutz reported 6 cases of so-called liver deaths 5 of which "died in a clinical state of uremia. The urine was scanty its specific gravity was high and it contained albumin and casts The non-protein nitrogen ranged between 46 and 240 and the creatinin between 2 3 and 8 6 mg per cent In 4 cases the condition developed after cholecystectomy 1 after massive traumatic injury to the liver and 1 from extensive destruction of the liver by carcinomatous metastases. The viscera revealed the same pattern of congestive and edematous appearances as we have described in shock. The kidneys were large pale and edematous they presented marked degenerative changes but no primary organic disease The authors attributed the renal changes to some potent toxin derived from the damaged liver

Boyce and McFetridge reported on a group of fatalities resulting from operations or injuries to the liver and/or biliary tract Some died in forty-eight to seventy two hours others had a normal postoperative course for four or five days followed by hyperpyrexia and death In the latter group "the outstanding clinical feature in all instances was deferred oliguria progressing to anuria and associated with typical changes in the blood chemistry chiefly a rise in the amount of non-protein nitrogen Postmortem examinations showed degenerative changes in the liver and in the tubules of the kidneys.

They noted the same clinical features in 6 cases of traumatic injury to the liver also after operations for pancreatitis in 4 cases

This article reviews some 34 reports in the literature bearing on the same subject In these it is noted that the same syndrome occurs after fracture of the skull, abdominal operations not involving the liver or biliary system, burns, intestinal obstruction and other conditions They commented on the parallelism between these and the "liver deaths" in that both showed the hepato-renal syndrome, *i e*, circulatory disturbances, hyperpyrexia and deficient renal function in which degeneration and/or necrosis of hepatic tissue and renal tubular degeneration were found at autopsy

Impairment of renal function is a prominent clinical feature after severe burns There is immediate oliguria or anuria, hemoglobin and albumin appear in the urine, and the urea, creatinin and non-protein nitrogen content of the blood rise progressively Underhill believed that the deficient renal elimination was due to hemoconcentration Christophe's studies on burns, both clinical and experimental, revealed marked renal deficiency as the chief feature when death did not occur soon In some cases the blood urea reached 400 mg per cent He believed this was due to true glomerulo-nephritis This interpretation is probably incorrect, since no evidence of nephritis persists in those who recover, but his data indicate the severity of the renal complication

The occurrence of shock after transfusion with incompatible blood was discussed in Chapter XIII Bordley reviewed 14 reported cases of severe illness after transfusions and compared the data with 3 cases reported by him, 2 of which recovered and 1 died The latter developed a severe immediate reaction with chill, fever, weakness, nausea and vomiting Seven days later the urine was scanty, it contained albumin and the specific gravity was high The non-protein nitrogen of the blood rose to 186 and the creatinin to 10 1, the chlorides and the alkaline reserve declined At necropsy the lungs were hyperemic and contained areas of early pneumonia The liver was large and showed fatty changes, parenchymatous degeneration, pigmentation and central necrosis The kidneys were enlarged, pale and edematous, microscopically they showed desquamation of epithelium, débris, pigmentation and infiltration with leukocytes In all of the cases there was urinary suppression and oliguria followed by nitrogen retention In the 11 fatal cases the uremic manifestations developed gradually after several days Renal degenerative changes were recorded in every instance when necropsy was made

Daniels, Leonard and Holtzman reported a group of 13 cases

in which transfusion of blood caused severe circulatory disturbance followed by renal insufficiency The non-protein nitrogen content of the blood ranged from 85 to 190 mg per cent The duration of illness in 7 cases ending fatally was from two to thirteen days The renal findings at necropsy examination in 4 of these consisted of edema, leukocytic infiltration, degeneration and necrosis of tubular epithelium, casts and pigmentation derived from hemoglobin. Gesse reported similar evidences of renal dysfunction after transfusions with incompatible blood

Goldring and Graef described 7 cases of "nephroses' with uremia following transfusions 3 of these ended fatally No organic renal disease was found at necropsy the kidneys showed only circulatory and degenerative changes The renal function returned to normal in those who recovered.

Recent reports (Mayon White and Solandt, Bywaters and Beall) on "crush injuries," resulting from the collapse of buildings during air raids in England, furnish highly significant instances of extrarenal uremia. Victims who had been pinioned under débris for hours showed hemoconcentration and other signs of shock when rescued The usual treatment for shock, including transfusions of blood or of serum maintained the blood volume and arterial pressure at adequate levels. Yet urination was scanty or suppressed, the non protein nitrogen of the blood rose progressively and the patients died after several days, during which the *syndrome of uremia* was the chief clinical feature In 1 case "early" amputation of the limb, performed thirty-six hours after the rescue, did not prevent the development of the syndrome I venture to suggest that amputation should have been done *immediately* after the rescue

The authors reported a subsequent case in which a young man aged twenty injured as described, was brought in The hemoglobin was 150 per cent blood pressure 110/70, pulse 136 and the temperature 97° He responded well to a transfusion of plasma but the syndrome developed as described The urea in the blood serum rose from 188 to 393 mg per cent and the potassium from 26 to 43 death occurred on the eighth day At necropsy the lungs were found congested and edematous focal hemorrhages and local cellular infiltrations were seen The muscles in the crushed area were pale and friable The mucosa of the stomach was hyperemic and contained minute hemorrhages. The liver was congested and showed parenchymatous degeneration The kidneys were pale

with prominent red streaks, microscopic examination showed edema and casts containing brown pigment

Mayon-White and Solandt reported an instance of the same syndrome which they summarized as follows "The case is reported of a patient who died from uremia following a type of injury that often produces shock The micropathology resembles that of incompatible transfusion Unlike similar cases reported in this issue (British Medical Journal) there can be no possibility here of incompatible transfusion, since no blood was given to our patient Herein lies the importance of this case and the reason for reporting it "

It was noted that the one feature which these cases had in common was extensive anemic necrosis of muscle Subsequently spectroscopic examination of the brown pigment found in the urine in these cases, showed it to be *myohemoglobin* This indicated that it was derived not from erythrocytes but from damaged muscle This evidence supports the explanation that absorption of products from traumatized tissues is a factor in the conditions resulting from "crush injuries "

The experimental production of shock with delayed death duplicates in all important particulars the syndrome of extra-renal uremia Long before that syndrome was recognized under that term, Whipple and his associates had produced it in animals by various means including proteose intoxication, sterile abscesses, staphylococcic infections, pleuritis, pancreatitis, intestinal obstruction and by other means They emphasized the marked retention of nitrogenous wastes—3 to 10 times the normal—deficient renal function and low blood pressure in these experiments "The dogs will die in twenty-four to thirty-six hours in a characteristic condition of surgical shock " Hashimoto described similar results during acute histamine poisoning The urea nitrogen increased by from 54 to 264 per cent and the urine was decreased in amount and highly concentrated Helwig and Schutz, also Boyce and McFetridge, produced in animals a condition resembling the hepato-renal syndrome by traumatic injury to liver and by introducing liver substance or extracts into the peritoneal cavity of dogs

Jeghers and Bakst made an excellent review of extrarenal uremia, correlating the observations of others with their own experiences, in various clinical types of disease More than 100 papers dealing with this and allied subjects are cited They speak of this as a disturbance of electrolytic and fluid balance

and believe its mechanism depends chiefly upon low blood pressure, hypochloremia and hyponatremia hemoconcentration ("dehydration"), hepatic damage, increased protein catabolism and secondary renal tubular damage They emphasize that in this syndrome the urine is scanty, concentrated and has a high specific gravity in contrast to opposite findings in uremia from chronic renal disease. Concerning the frequency and severity of this condition they state "In routine clinical practice an azotemia is much more commonly due to the mechanisms discussed in this paper than to organic renal disease Another misconception is that the blood non protein nitrogen in extrarenal azotemia rarely increased to a degree comparable with that seen in organic renal disease. Quite the opposite is true Values of 100 or even 200 mg per cent are common" They cite a case reported by Fishberg, in which the non-protein nitrogen rose to 400 mg per cent in three days and decreased with equal rapidity as recovery occurred.

The types of conditions in which extrarenal uremia occurred are of particular significance in the present discussion These included pyloric obstruction, the so-called liver kidney syndrome which is related to toxic jaundice perforated peptic ulcer peritonitis yellow fever, Weil's disease, lobar pneumonia shock from various causes including postoperative, reactions after transfusions, allergic reactions, urticaria Addison's disease diabetes mellitus, drug intoxications acute pancreatitis and burns They found low arterial blood pressure, urine of low volume and high concentration, hypochloremia, high non protein nitrogen and "dehydration" of the blood—hemoconcentration—of great value in the clinical differentiation of this from other conditions They emphasize the significance of an increase in the erythrocytic count hemoglobin content or in the hematocrit value as a criterion and express a preference for the latter as the simplest and perhaps the most accurate. The obvious relationships between these conditions and the mechanism of shock require no emphasis.

In a number of cases, some data from necropsy examinations were given These pertained chiefly to the primary clinical condition and to the renal findings. The latter included swollen engorged sometimes edematous parenchyma, granular débris and occasional casts. Neither glomerulonephritis nor other primary organic renal disease was found In a few cases capillary hemorrhages were noted and hepatic necroses in some It is significant that "bronchopneumonia" was a terminal event as revealed by

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the necropsy The cases reported by Brown and his associates (p 183) illustrate both the syndrome of extrarenal uremia and terminal pneumonia in sublethal shock

Medical literature contains numerous reports of deficient renal excretion, associated with circulatory deficiency of the shock type No further analysis of the reports will be made here, readers desiring additional data will find references in the articles already cited Records of necropsies in Jefferson Hospital indicate that this syndrome has a percentile occurrence much higher than that of glomerulonephritis The conditions presented include severe acute infections of various types, intoxications such as acute hepatic necrosis, toxic jaundice, diabetes mellitus, eclampsia, so-called "liver deaths," intestinal obstruction, peritonitis, pancreatitis, cerebral lesions such as abscess or hemorrhage, drug poisoning as with cincophen or adulterated spirituous liquor, burns, and post-operative surgical complications Unfortunately, in the majority of cases, neither the attending physician nor the interne had sensed that a disturbance of fluid balance or of the circulation was implicated, accordingly blood examinations for hemoconcentration were not made In numerous instances the term *uremia* was written, as a chief or secondary clinical diagnosis, on the history or on the death certificate In other instances, records of urinalysis and chemical examinations of the blood indicated deficient renal function which at autopsy was shown not to arise from organic renal disease

The necropsy in these cases regularly revealed capillo-venous congestion of the viscera, frequently there were slight or moderate effusions of fluid in the serous cavities and varying degrees of edema in the soft tissues The kidneys were usually above normal size and showed diffuse congestion Microscopically, the tubules showed parenchymatous degeneration, sometimes necrosis, of the epithelium, capillary congestion and there was granular débris, sometimes casts, in the tubular lumina (See Fig 24) A terminal pneumonia in hyperemic edematous lungs, as described in the preceding chapter, was present in almost every case

Let it be reemphasized that albuminuria, oliguria, concentrated urine and retention of nitrogenous wastes are regular features of both clinical and experimental shock Also that the characteristic pathology of shock includes acute degeneration and necrosis of the liver, congestion and degeneration of the renal parenchyma The parallelism between these features in acute shock and the syndrome of extrarenal uremia is striking It strongly supports the interpretation that the latter is a syndrome which develops

frequently when shock of sublethal degree occurs or when shock does not lead immediately to death

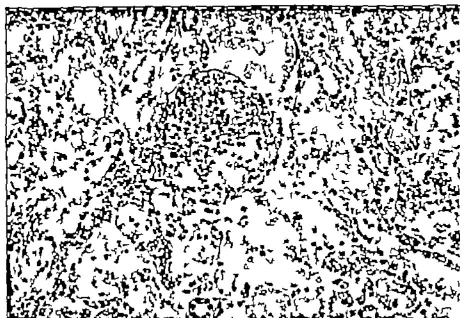


FIG. 24—Photomicrograph of kidney after death by extrarenal uremia. Intense congestion, tubular dilatation débris, granular degeneration and beginning epithelial necrosis are shown. The capsular space and some of the tubules contain erythrocytes.

THE MECHANISM OF EXTRARENAL UREMIA[1]

The syndrome under consideration has been recognized as such only since about 1923 The clinical and pathologic features seem to coincide with those of "acute parenchymatous nephritis" in the nomenclature of the past epoch The low sodium chloride content of the blood gives rise to the term *hypochloremic uremia* because some have supposed the low blood chlorides play an important rôle in causing the disturbance Several authors support this theory while others believe that hypochloremia *per se* is not of etiologic importance

The low content of sodium chloride of the blood during shock from various causes was explained (pp 35–37) together with other

[1] A moderate increase in the non-protein nitrogen of the blood occurs as a result of hemorrhages into the gastro-intestinal tract (Schiff and associates also Chunn and Harkins, for discussions) This increase seldom exceeds 50 mg per 100 cc of blood and it never approaches the degree of nitrogen retention seen in sublethal shock. The authors mentioned produced the condition experimentally by feeding blood to animals and to human subjects. Apparently alimentary azotemia results from the digestion and absorption of blood it is not accompanied by impairment of renal function.

disturbances in the concentration of electrolytes arising from injury to cells in general These are effects regularly associated with that syndrome and the supposition that they of themselves cause renal dysfunction, lacks experimental support.

Marriott (1923), reviewing the subject of anhydremia (hemoconcentration) found this was associated with greatly diminished renal secretion and even with anuria The specific gravity of the urine ranged up to 1 040 There was marked retention of nitrogenous wastes in the blood which was not due to organic renal impairment but which resulted from the inability of the kidneys to secrete urine from concentrated blood This disfunction returned to normal when water balance was reestablished

In weighing the evidence, Bell found little justification for the term *hypochloremic uremia* and for the supposition that this plays an important rôle in its development He pointed out that urine is formed primarily by filtration of fluid through the glomerular endothelium and that the blood normally resists concentration, *i e*, abnormal concentration of the blood retards or prevents filtration Lassen and Husfeldt emphasize the low blood pressure as producing this same effect, and Jeghers and Bakst have corroborated this observation Gomori and Podhydsky investigated experimentally the supposition that extrarenal uremia is due to hypochloremia Their results led to the conclusion that the cause is exsiccosis (concentration of the blood) plus reduced blood pressure "The direct cause of the extrarenal azotemia is not to be found in a chloride loss but in changes in hemodynamic factors "

It is well known that the rate of filtration varies directly with the capillary blood pressure and that the osmotic pressure of the plasma colloids opposes filtration Hence both the increased concentration of the blood and the decreased blood pressure would retard or prevent the filtration by which the urine is formed. It is equally well known that variations in the concentration of sodium chloride have little to do with this process Electrolytes readily pass by diffusion in either direction through a semipermeable membrane such as endothelium Hence it is difficult to see by what mechanism the hypochloremia could affect the formation of urine

In the treatment of "crush injuries," *i. e*, sublethal shock resulting from compression necrosis of muscles, the deficiency of renal function progressed even though adequate blood pressure was maintained and the hemoconcentration was reduced by

infusions of fluid This fact suggests that the functional impairment may arise partly from some factor other than low blood pressure and hemoconcentration, that perhaps the same toxic agents which caused endothelial damage and circulatory disturbance, also caused parenchymal degeneration and functional deficiency of the kidneys

Summary —Oliguria, albuminuria parenchymatous renal degeneration and deficiency of renal function are regular features accompanying both clinical and experimental shock.

When the shock syndrome leads to death promptly, the fatal outcome is due to circulatory failure When circulatory deficiency of sublethal degree persists for a time, then evidence of impaired renal function appears which may culminate in the syndrome of *extrarenal uremia*

Postmortem examination reveals no preëxisting renal disease but shows only parenchymal degeneration sometimes necrosis of tubular epithelium, edema, dilatation of tubules, and pigmentation In some cases slight leukocytic infiltration, casts and débris within the tubules, have been found. No permanent impairment of function remains in those who recover

Extrarenal uremia occurs commonly in sublethal shock originating from diverse causes but the exact mechanism of its development has not been shown It appears that hypochloremia is not itself a cause for the deficiency of renal function but should be regarded merely as one of the effects of shock.

Both low blood pressure and increased concentration of the blood interfere with the filtration function of the glomeruli These may impair the renal function and hinder elimination

It is possible that parenchymal degeneration, resulting either from anoxia or from toxic effects, may also impair the function of the kidneys. The exact mechanism by which extrarenal uremia develops as a complication of sublethal shock requires further investigation.

CHAPTER XVI

ADRENAL CORTICAL INSUFFICIENCY

Relationship to Circulatory Deficiency.—I shall not attempt here an analysis or summary of information concerning the physiology of the adrenal cortex There is evidence that one important cortical function is closely related to endothelial and capillary physiology This evidence is of three-fold interest. it has a bearing on the dynamics of shock, it illuminates the disturbance of circulation which develops in acute or chronic adrenal cortical deficiency, it supplies the rationale for the use of adrenal cortical hormone in the treatment of shock

Selye regards the adrenal cortical hormone as a major item in the defense of the body against systemic injury of various kinds This view is supported by the depletion of the cortical cells during and after such emergencies and by the hyperplasia of them as recovery occurs This evidence was so impressive that he explains shock as a deficiency of the defensive reactions, particularly of the adrenals (see p 95)

It has long been known that complete adrenalectomy produces fatal disorders of systemic functions These cannot be relieved or prevented by injections of epinephrin, hence the disturbances are due to lack of the cortical rather than of the medullary secretion Adrenalectomized dogs lose appetitite, become weak and listless, there are vomiting, diarrhea, marked depression, feeble pulse, low blood pressure and metabolism, and other manifestions like those of shock Swingle and his associates made an itemized comparison of the physiologic disturbances which result from adrenal cortical deficiency with those of traumatic or surgical shock They found points of identity between the two conditions (Table 3)

Some of the authors recorded the appearances seen in the viscera after death from adrenal cortical insufficiency Banting and Gairns found the superficial veins collapsed and bloodless so that it was difficult to secure specimens of blood by venipuncture The blood was dark, viscid, slow to clot and its plasma volume was reduced They described marked congestion of the abdominal viscera, there was bloody or brownish fluid within the gastro-intestinal tract and the mucous surfaces showed capillary engorgement and petechial [illegible] s The occurrence of gastric

ulcers was a common finding There was marked congestion of the liver, and the hepatic cells showed degeneration and necrosis The parenchyma of the kidneys was congested, hemorrhagic and showed marked acute degeneration The similarities between these findings and those seen after fatal burns deserve emphasis.

TABLE 3 —CONDITIONS EXISTING IN ADRENAL CORTICAL INSUFFICIENCY (ANIMALS) AND TRAUMATIC SHOCK (MAN)

1	Blood volume	Decreased
2	Blood pressure	Decreased
3	Hemoglobin	Increased
4	Hematocrit reading	Increased
5	Red cell count	Increased
6.	Venous pressure	Decreased
7	Volume flow of blood	Decreased
8.	Viscosity of blood	Increased
9	Hemoconcentration	Increased
10	Cardiac output	Decreased
11	Venous return to right heart	Decreased
12	Heart rate	Increased
13	Weak rapid pulse	Present
14.	Vasoconstriction	Present
15	Ability to dilute blood	Reduced or absent
16	Blood non protein nitrogen and urea	Increased
17	Alkali reserve	Decreased
18	Basal metabolism	Decreased
19	Blood sugar	Decreased in adrenal insufficiency; Normal or above in shock
20	Body temperature	Decreased
21	Vasoconstrictor drugs	Ineffective
22.	Fluids given intravenously	Beneficial
23	Vasomotor activity	Apparently normal
24	Sensitivity to painful stimuli	Decreased
25	Sensitivity to cold	Increased
26	Sensitivity to anesthetics	Increased
27	Sensitivity to histamine	Increased in adrenal insufficiency
28.	Sensitivity to infections and toxins	Increased
29	Renal function	Impaired
30.	Sensitivity to hemorrhage	Increased
31	Sensitivity to trauma and operations	Increased

Several writers have reported hemoconcentration after adrenalectomy Lucas corroborated this feature and recorded erythrocytic counts ranging up to 10 000 000 Rogoff and Stewart later confirmed also the congestive ecchymotic and degenerative changes described by Banting and Gairns in the mucosæ and parenchymatous organs. They attributed the visceral engorgement to "intoxication" rather than to passive congestion. They also recorded a high incidence of gastric ulcers.

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Enlargement of the thymus and hyperplasia of lymphoid tissue throughout the body have been noted by many writers when death was delayed several days or weeks after adrenalectomy Selye has investigated extensively the biologic phenomena which occur when the body is subjected to stimuli (injurious conditions) to which it is not adapted The "alarm reaction" (mechanism of defense) includes a number of factors, important among which are the ductless glands He has found evidence of increased adrenal cortical activity as an essential feature in the immediate reaction to deleterious agents of various kinds Simultaneously the thymus undergoes conspicuous regressive or involutionary changes which are most pronounced during the recovery phase of the reaction when adrenal cortical hyperplasia is maximal Selye is impressed by the fact that removal of the adrenals prevents thymic involution, he states that involution of the thymus cannot occur in the absence of adrenal cortical hormones The importance of this feature will be discussed subsequently in relation to status lymphaticus and to Addison's disease

A comparison of all these items with those which occur characteristically in shock from trauma or from other causes, lends support to Swingle's suggestion that adrenal cortical insufficiency is a fundamental factor in the mechanism of shock Also Selye's discussion of the "alarm reaction" is in line with this evidence Further significance is contributed by the fact that the administration of cortical hormone restores the animals to circulatory efficiency and to a normal physiologic state This can be maintained indefinitely by supplying cortical extract artificially but if the treatment is interrupted a condition identical with shock in all particulars, develops However, one important fact seems to invalidate the supposition that deficiency of cortical hormone is a primary etiologic feature in shock The circulatory deficiency described does not develop immediately after adrenalectomy Rogoff and Stewart reported an average survival time of seven days in 74 dogs in which the adrenals were carefully excised in a two-stage operation Accordingly if trauma or burns should cause *complete* exhaustion or inhibition of the cortical function, the effects should not be shown for several days The fact that shock develops within a few hours after burns or trauma renders untenable the hypothesis that this effect could be caused primarily by deficient adrenal cortical function

We (1936) suggested another explanation for the phenomena described

"One function of the hormone of the adrenal cortex may be to maintain the tonus of the capillaries and venules. Atony of these is regularly present in shock, and is the major factor in its development. These vessels become atonic and relaxed after a time when deprived of cortical hormone. Then a disparity between the volume of the blood and the capacity of the blood vessels develops because of the inability of the vascular system to contract with its normal tonus on the contained blood. Tonus and circulatory efficiency are restored by supplying the animal with extract of adrenal cortex. Loss of tonus and circulatory inefficiency reappear when this extract is withheld. Animals maintained on a minimal amount of the hormone of the adrenal cortex become abnormally susceptible to various agents and conditions which produce shock (Swingle and his collaborators). Apparently the minute vessels are more easily rendered atonic when supplied insufficiently with the hormone.

"The function of other glands of internal secretion as well as the adrenals has been studied physiologically by noting the disturbances which follow their extirpation. If those disturbances disappear when an extract of the gland is supplied artificially, a function of that gland is thereby demonstrated. Similar logic might be applied to the results of experimentation on the adrenal cortex. The hypothesis that one of its functions is to maintain the physiologic tonus of the capillaries and venules deserves consideration."

This interpretation of the mechanism by which deficiency of adrenal cortical function is related to endothelial tonus and thereby to shock, was subsequently endorsed by Swingle and his associates (1938). They "attribute the cause of death from adrenal insufficiency to capillary atony, with resulting dilatation, stasis and peripheral vascular stagnation, and believe that the cortical hormone is concerned with the maintenance of capillary tone and therefore regulatory control of the volume capacity of the circulatory system."

Kendall (1941) states that disturbances in the distribution and excretion of inorganic ions is the immediate cause of the symptoms of adrenal deficiency. This ultimately involves hemoconcentration and the inability of the vascular system to retain water. Control of permeability and of the transfer of water and ions between extra-cellular and intra-cellular phases are given first place among adrenal cortical functions. Hemoconcentration observed during adrenal deficiency is due to the absence of the adrenal hormones which are essential for the integrity of the capillary bed. In the absence of the hormones the normal volume of the circulating blood cannot be maintained.

It appears that *control of permeability* is an adrenal cortical function of the highest importance. This permeability pertains both to endothelium and to cells. Abnormal permeability of the

former leads to disturbances of fluid balance, of absorption and of the systemic circulation Abnormal permeability of cells leads to disturbances of the concentration of electrolytes as discussed in Chapter II The latter produce the variations in the concentration of various chemical substances seen in shock arising from various causes including adrenal cortical deficiency

Subnormal Cortical Function.—Studies have been made on animals after subtotal adrenalectomy and on those supplied with an inadequate amount of the cortical hormone Such animals present a characteristic syndrome of dysfunctions They are easily affected by fatigue, hemorrhage, trauma, infections and by changes in temperature The results of such observations are summarized by Grollman

"Adrenalectomized animals are not only hypersensitive to such extraneous influences as excessive heat or cold, muscular exhaustion, excitement, etc , but they also show an abnormal sensitivity to various drugs and toxic agents This hypersensitivity has been demonstrated for histamine, curare, strychnine, morphine, nicotine, acetonitrile, adrenalin, diphtheria or tetanus toxins, cobra venom, typhoid or staphylococcus vaccines, foreign proteins and other toxic agencies In many cases this hypersensitivity is very marked "

The reproductive function is greatly depressed or is entirely obliterated There are no manifestations of the mating instinct and œstrus is absent in females after extirpation of the adrenals All these features have a striking similarity to the clinical manifestations of status lymphaticus and of Addison's disease A further point of similarity is the hyperplasia of thymus and of lymph nodes which is associated with each of these conditions These facts have led Jaffe, Marine and others to regard subnormal adrenal cortical function in animals as the experimental production of status lymphaticus

"Suprarenalectomy causes the greatest lowering of resistance or increase in susceptibility of any known experimental procedure When this knowledge is added to the fact that suprarenalectomy causes a rapid regeneration of the thymus and lymphoid tissue—a true experimental status lymphaticus —in animals the conclusion that a deficiency of some suprarenal or gonadal function is a major factor in the etiology of status lymphaticus seems justified " (Marine)

STATUS LYMPHATICUS

Medical literature on this subject is characterized by confusion rather than by clarity The occasional occurrence of sudden death without adequate cause has led to unconvincing theorization

and speculation The fact that necropsy in such instances usually shows hyperplasia of lymphoid tissue, especially *thymic*, naturally directed attention to that feature—hence the term *Status Thymico-lymphaticus*

A reëxamination of the theories based upon this feature will not be profitable Greenwood and Woods reviewed the existing evidence and concluded that the conception of this as a disease entity belongs in the realm of medical mythology and that it is as accurate to assign such deaths to the visitation of God as to status lymphaticus. Young and Turnbull made a formal investigation under the auspices of the British Medical Research Council Their survey led to the conclusion that the facts elicited afford no evidence that so-called status thymico-lymphaticus has any existence as a pathological entity '

These appraisals obviously are too inclusive but they may be applied to the theories incriminating the enlarged thymus as a lethal agent. There is complete lack of evidence that the thymus itself is a factor in causing death, but the mechanism of these unexplained phenomena merits investigation rather than disregard Man s most perplexing problems are not solved merely by denying their existence One such problem is presented by the following simple and well attested facts

First that a small percentage of human beings present a group of associated anatomic features differing characteristically from the normal These include a generalized hyperplasia of lymphoid tissue lymphoid infiltration of other tissues moderate lymphocytosis in the blood hypoplasia of heart and arteries, of reproductive organs and of chromaffin tissues and certain variations in physical configuration Symmers found this combination of physical traits present in 6 2 per cent of subjects in a series of 4 000 necropsy examinations It occurred in males 6 times oftener than in females.

The second fact is that a few individuals are highly vulnerable to infections intoxications and injuries of diverse kinds and that these persons may die unexpectedly from trivial or inadequate causes Such cases occur almost exclusively among those of the anatomic group described This indicates a relationship which is not adequately explained as coincidence or chance The problem of status lymphaticus consists in demonstrating the nature of this relationship

Deaths from apparently insufficient causes occur most often in children and may follow minor injuries, as cuts or bruises, surgical procedures as opening an abscess removing a splinter tonsillec

tomy, the extraction of a tooth, anesthesia, vaccination or hypodermic injections Minor ailments and infections, which do not imperil life in normal children, may cause death rapidly or suddenly in the group referred to

The antemortem manifestation described in such cases bear a remarkable resemblance to those of shock This is illustrated by the fact that frequently the attending physician ascribes the acute illness and death to *anaphylaxis* even though no foreign protein has been introduced This resemblance is so marked that Symmers proposed anaphylaxis as the cause He found small necrotic foci in the lymphoid tissues and suggested that the subject had become allergic to the protein of his own tissues(!) and thereby developed a reaction of the anaphylactic type We have found focal necroses in lymphoid and parenchymatous tissues after death by shock variously produced It is our belief that these are results rather than causes of the reactions which led to death

It is significant also that the necropsy findings usually include visceral congestion and edema in addition to lymphoid hyperplasia and other features mentioned earlier in this discussion Richardson (1905) reported the findings after death in a boy aged nine who died suddenly after the suturing of a small cut in the skin The thymus and lymph nodes were hyperplastic and the aorta was thin and hypoplastic The lungs were congested and contained small hemorrhagic areas The bronchial mucosa was congested, swollen and the lumina contained blood-tinged fluid He remarked upon the fact that in this and similar cases the adrenals were small and flat In one instance no chromaffin substance at all was found Many of the records describe circulatory and lymphoid changes but omit any notations concerning the adrenal bodies Observations on this feature in the large series of cases examined by Symmers, would be most valuable had they been published

Waldbott analysed the clinical data and morphologic changes recorded by other pathologists in 34 cases which, after critical scrutiny, were regarded as acceptable cases of status thymicolymphaticus In one instance the thymus was not enlarged, in the others the weight of the thymus ranged between 15 and 85 gms

"The most constant and characteristic changes were present in the lungs On gross examination there was a marked increase in weight and exudation of fluid from the cut surface Some areas were crepitant, others distended, others edematous The microscopic sections of all 34 cases showed

areas of marked dilatation of the capillary blood vessels. In some instances the capillaries appeared to be packed with blood cells In other areas there was extravasation of blood cells or exudation of edematous fluid into the alveolar spaces and secondary bronchi.

Petchial hemorrhages were described in serous surfaces and in certain of the viscera in 29 of the cases. Marked hypoplasia of the adrenals was noted in most of the records. Waldbott commented on the similarity of the circulatory changes to those seen after death by anaphylaxis as indicating some kinship between those conditions Certainly the circulatory changes noted were of the same pattern as those seen after shock from various causes. His analysis of cases confirms important interpretations made earlier by Marine The latter defined status lymphaticus as

"A constitutional defect usually congenital (though it may be acquired) dependent upon an inadequacy of the suprarenals, sex glands and autonomic nervous system and associated with lowered resistance or increased susceptibility to a great variety of non-specific physical and chemical agents Anatomically it is characterized by delayed involution or hyperplasia of the thymus, hypertrophy and hyperplasia of the lymph glands and lymphoid tissue of the various organs, underdevelopment of the chromaffin gonadal (suprarenal cortex, interstitial cells of the testis and ovaries) and cardiovascular systems, and certain peculiarities of external configuration "

The evidence which we have cited supports a hypothesis explaining many perplexing features in the syndrome of status lymphaticus. That condition has many features in common with experimental adrenal cortical insufficiency Both are characterized by a high degree of susceptibility to various injurious agents and conditions including trauma drugs, surgical procedures and infections In both there is hypoplasia of the gonads and depression of the reproductive function Hyperplasia of the thymus and of lymphoid tissue in general are prominent features. Lowered resistance to various agents is manifested by signs like those of anaphylaxis death is preceded by acute circulatory deficiency and the necropsy findings are identical with those which are characteristic of shock.

These resemblances seem to justify the conclusion expressed by both Jaffe and Marine, that the picture presented by adrenal cortical deficiency in animals may justly be considered as the experimental production of status lymphaticus. This hypothesis is in harmony with the evidence that a highly important function of the adrenal cortex has to do with defense against various unfavorable conditions and that *one* function of this hormone is the maintenance of endothelial tonus. Deficiency of cortical

function, produced experimentally or occurring as a congenital defect, predisposes to loss of endothelial tonus, to dilatation and hyperpermeability leading to acute circulatory failure of the shock type

This should be considered as a reasonable working hypothesis which may be either corroborated or invalidated by the acquisition of additional evidence

ADDISON'S DISEASE

It is well known that extensive destruction of adrenal tissue by tuberculosis or other disease, produces a characteristic group of systemic disturbances These have many points of similarity with experimental adrenal cortical deficiency There are marked weakness, fatigability and loss of weight Vomiting, diarrhea and other disturbances of digestive function are regularly present Dyspnea, low blood pressure, rapid feeble pulse and a tendency to syncope or collapse are prominent in advanced stages of the condition The basal metabolism is low and the renal function deficient Such patients have a markedly lowered resistance to infections and to other hazards, they do not withstand extremes of temperature, exertion, anesthesia, or minor surgical procedures and they often are hypersusceptible to the action of drugs Rowntree noted that signs of shock were prominent in the crises of the disease or shortly before death The flesh lost its normal turgor and became cold to the touch, the temperature became subnormal, the peripheral veins were collapsed and relatively bloodless, it was difficult to secure blood by venipuncture and the blood was abnormally concentrated

Most of the published data from necropsy examinations pertained to the destruction of the adrenal glands by atrophy or disease, the pigmentation of the skin and the evidence of tuberculosis elsewhere in the body When complete findings are published they usually include marked "passive congestion of the lungs" and varying degrees of visceral congestion, often with edema It is significant that many cases show "bronchopneumonia" and that clinically this is often the terminal event (see Chapter XIV) Frequently persistent or hyperplastic thymus and hyperplasia of other lymphoid tissues are found

The similarities between this syndrome and the conditions of animals lacking in adrenal cortical hormone are numerous Those similarities include also the response to the administration of

cortical extract Rowntree and his associates found that injections of the hormone caused the manifestations of adrenal deficiency to disappear in a spectacular manner but epinephrin had no such effects. The benefits derived from cortical extract were most marked in the acute stages or the crises of the disease The vomiting and diarrhea ceased, the appetite improved, metabolism rose to normal, the strength and endurance increased There was relief from pain and fatigue and the mental state changed from depression to hope and optimism The patients withstood anesthesia and operative procedures such as usually prove fatal in untreated cases of Addison's disease Patients in an acute stage of shock sometimes responded in a manner described as dramatic The circulation returned to normal efficiency and the improvement just described followed.

It is not strange that Addison's disease in man and adrenal cortical deficiency in animals should have in common many physiologic disturbances and that many of these should be relieved by supplying the subjects with the hormone which they lacked But attention should be called to several resemblances between Addison's disease and status lymphaticus

Star (1895) commented upon thymic and lymphoid hyperplasia in Addison's disease and Wiesel (1903) made similar observations He attributed status lymphaticus to hypoplasia of the chromaffin system. Hedinger (1907) commented on the fact that both Addison s disease and status lymphaticus are characterized by abnormal susceptibility to injurious agents and by thymic and lymphoid hyperplasia he found hyperplasia of these tissues at necropsy in 12 out of 15 cases of Addison's disease he believed that both diseases are related and that they originate in deficiencies in the chromaffin system

An examination of the protocols of necropsy examinations in Addison's disease reveals that hyperplasia of the thymus and of lymphoid tissue was found almost regularly Another striking resemblance to status lymphaticus is the hypersusceptibility to injury, infections and to various noxious agents Death may occur from trivial or apparently insufficient cause in each condition and it usually is preceded by evidences of circulatory disturbances of the type seen in shock These considerations lend support to the hypothesis that status lymphaticus may be explained ultimately as a congenital deficiency of the endocrine glands involving, among others the adrenal cortical secretion

The usefulness of adrenal cortical extract in cases of Addison's

disease has been demonstrated beyond question Its therapeutic use in the prevention and treatment of shock is still in the experimental stage as will be discussed in a later chapter The evidence seems sufficient to justify the trial of cortical extract for the prevention of shock when those having the anatomic characteristics described by Symmers, acquire infections or are to be subjected to surgical procedures

Summary —Lack of adrenal cortical hormone is followed by the development of the shock syndrome This presents the same functional disorders, chemical alterations and pathologic changes in the viscera as are produced by shock originating otherwise

In adrenalectomized animals, shock develops gradually after the lapse of several days This and other evidence indicate that one function of the adrenal cortical hormone is to maintain the normal tonus and semipermeability of endothelium

Adrenalectomy causes hyperplasia of lymphoid tissue, including the thymus This is accompanied by greatly increased susceptibility to various types of noxious agents Many facts support the interpretation that status lymphaticus is essentially a condition of deficient adrenal cortical function Likewise there are many similarities between these conditions and Addison's disease

The benefits which follow the administration of adrenal cortical extract in Addison's disease support the suggestion that cases of status lymphaticus should be given adrenal cortical extract before subjecting them to minor surgical procedures

CHAPTER XVII

RECAPITULATION

BEFORE discussing the prevention and management of shock, a resumé may be helpful in integrating the previous discussions into an intelligible picture In the *Foreword* to Part I the *Dynamics of Shock*, it was set forth that the existing lack of agreement originated chiefly from 4 major sources The first of these was inadequate knowledge of endothelial function and reactions and of circulatory disturbances originating in the capillaries A comprehension of these has contributed immeasurably to an understanding of shock resulting from various causes also it has clarified the disturbance of fluid balance which is regularly associated with it An additional obstacle to agreement has been that many surgeons regarded traumatic shock as a distinct entity—a condition *sui generis*—and did not comprehend its relationship to circulatory failure of exactly the same type originating under other conditions.

The second major cause for confusion was the failure to distinguish between shock and the effects of hemorrhages. Loss of blood is frequently an associated feature when shock has resulted from physical trauma, and its contributory effect is of the highest importance But the effects of uncomplicated hemorrhages present numerous features opposite in character from those which constitute the syndrome of shock.

Variations in blood pressure used as a criterion and failure to consider the depressor effects of anesthesia and of losses of blood, have led to undependable conclusions concerning the effects of absorption A revision of experimental technique employing controls which obviated these sources of error has demonstrated that the absorption of products derived from damaged tissues independent of narcosis and of hemorrhage will produce the complete syndrome of shock.

Last but perhaps not least of the causes for confusion was failure to apply to the problem the methods used by pathologists Hemoconcentration during life, and the presence of engorged capillaries stasis petechiæ and edema after death indicate beyond peradventure that endothelial damage is a dynamic factor of the highest importance Shock like other conditions of disease, is

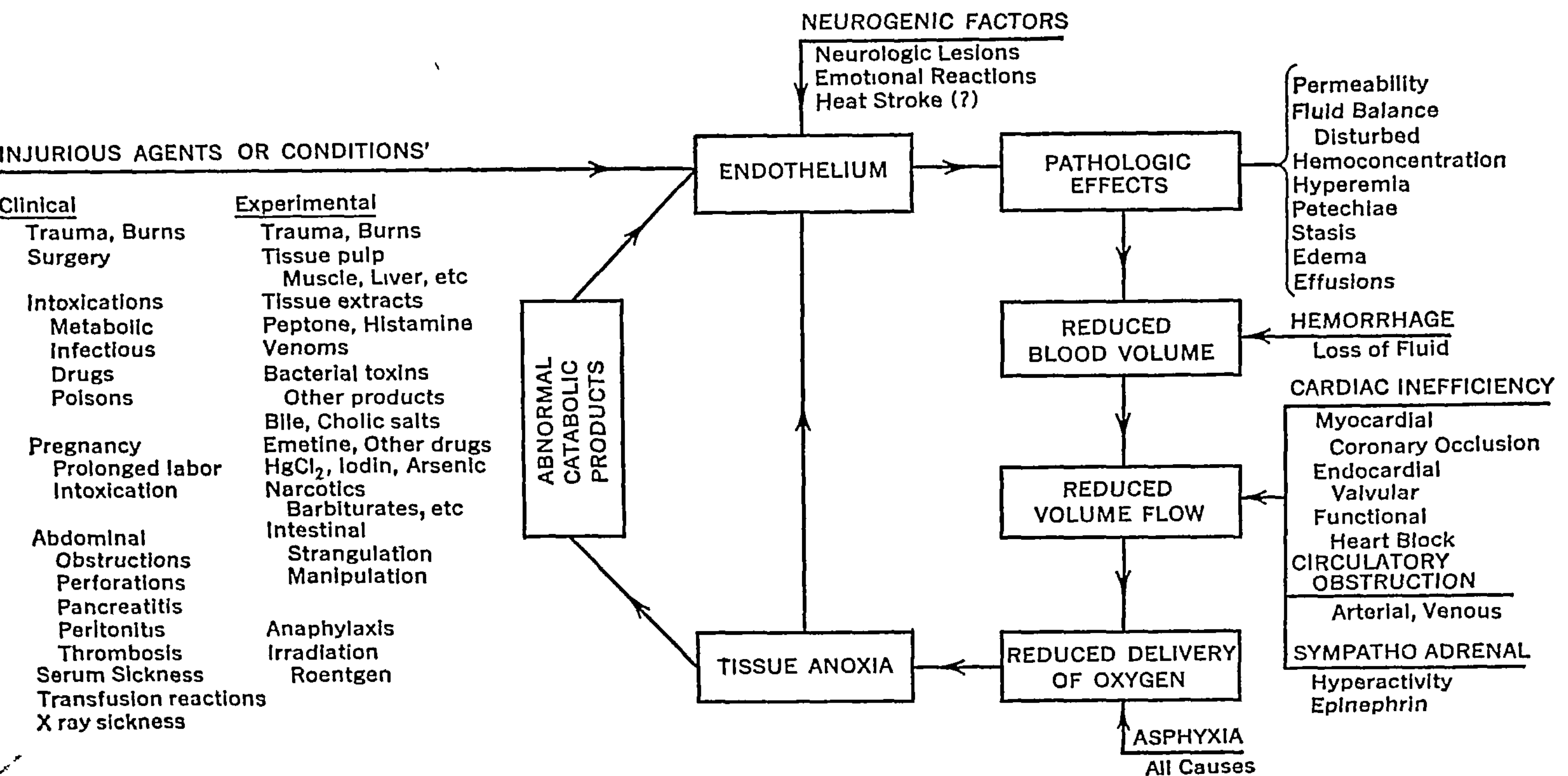


FIG 25 —"The Cycle of Death" This diagram shows relationships between chief and contributory factors in the mechanism of shock For a discussion of this vicious circle, see pp 209–212

accompanied by a pattern of morphologic changes which are related etiologically to its mechanism of origin and which indicate that dysfunction of endothelium is a major factor in its development

In view of the character and magnitude of these sources for confusion it is not strange that final clarification of the problem has been delayed When these causes have been recognized and obviated, it becomes a simple matter to assemble the related facts and reactions into an intelligible picture Figure 25 presents that picture as we see it.

THE CYCLE OF DEATH

The functions of the capillaries in serving the needs of the tissues, require that they be delicately responsive to lack of oxygen and to the presence of metabolites But they are equally sensitive to various noxious agents Because of this sensitivity, the capillary endothelium is a most vulnerable structure, highly susceptible to injury and, in response to it, giving origin to serious disturbances of the circulatory function

In discussing the diagram (Fig 25) on p 208, the term *Capillary Atony* will be used to include the pathologic effects resulting from *endothelial damage* The effects of anoxia upon endothelium and the initiation of a vicious circle were set forth in Chapter IV It was shown that the two major factors in this cycle are *Anoxia* and *Capillary Atony*, also that these factors are reciprocal because the effect of either of them gives origin to the other It is appropriate here to consider the various ways in which this circulatory disturbance may develop and the contributory influences of other factors The diagram shows the relationship of these factors to the genesis of shock

Under Agents or Conditions Injurious to Capillaries are listed the various clinical conditions and experimental agents which will give rise to shock I have included under clinical conditions only those in which the case histories showed that death resulted from shock or circulatory collapse and in which the necropsy findings were characteristically those of shock. Also under experimental agents are listed only those with which I have had personal experience In each instance these agents have produced the shock syndrome in animals accompanied by hemoconcentration, followed by death from circulatory failure, and in each instance the postmortem findings were those which regularly result from

shock Doubtless many other agents than those listed would have a similar circulatory effect if given to animals under suitable conditions Apparently numerous diverse clinical conditions and experimental agents may cause injury to endothelium and, by virtue of that effect, may produce *Capillary Atony* with the results as indicated in the diagram

It has been observed that lesions of the central nervous system, such as hemorrhage, tumors and other organic lesions, and the effects of direct trauma or surgical operations involving various portions of the brain, often produce shock-like manifestations Examinations of the blood in such instances have shown hemoconcentration and the viscera after death present typically the circulatory changes of shock Death from circulatory failure occurs occasionally in various forms of psychopathy in which demonstrable lesions are lacking In such cases the same congestive and edematous conditions of the viscera are found It is known that local edema sometimes results from disturbances of innervation, and that the edema fluid resembles plasma in its composition All these observations indicate that *Endothelial damage* may result from disturbances arising from nerve agencies

Heat stroke is accompanied by circulatory collapse, sometimes so severe as to end fatally The postmortem findings duplicate exactly those which we have found after experimental shock produced by various means The mechanism by which heat stroke causes circulatory failure has not been shown, but many believe it to be through effects upon the central nervous system It is evident that the same cycle, whose effects are seen in many other grave clinical conditions, is operative here

Endothelial damage, regardless of its origin, produces directly the *Pathology of Shock* These changes consist of dilatation and engorgement of venules and capillaries in the viscera, stasis, petechiæ, edema and effusions The sequestration of blood by stasis lowers the *effective* blood volume, and the edema, effusions and hemorrhages lower the *actual* blood volume These conditions tend to cause a disparity between the volume of blood and the volume-capacity of the vascular system Physiologic compensation for *Reduced Volume of Blood* is accomplished in part by vasoconstriction of the arteries This directly causes a *Reduced Volume Flow*, thereby causing *Reduced Delivery of Oxygen* to the tissues and *Tissue Anoxia* This latter condition produces *Endothelial injury* and completes the cycle, the effects of which become irreversible if not relieved soon

It is important to recognize that the operation of the vicious circle may start at other points than *Endothelial injury* or *Tissue Anoxia* For example *Reduced Blood Volume* from any cause, will be accompanied by a reduction of the *Volume Flow* and if sufficient in degree, will decrease the delivery of oxygen and lead to *Anoxia* thereby initiating the operation of the cycle Loss of blood by hemorrhage and loss of fluid by vomiting purging or by perspiration, may reduce the blood volume if the mechanism of fluid balance is seriously disturbed So long as the vascular endothelium is functioning normally such loss of volume is readily compensated by absorption of fluid from the gastro-intestinal tract and from the tissues. The ability to absorb fluid and the entire mechanism of "water balance are dependent upon a normal state of the endothelium Hence loss of fluid by any route may not be restored if abnormal permeability of endothelium has developed

Any condition which causes a reduction of the *Volume Flow* below physiologic limits may so decrease the delivery of oxygen as to cause *Tissue Anoxia* and thereby may initiate the vicious circle Examples of this are seen in the production of shock experimentally by large doses of adrenalin or by retarding the circulation mechanically as in the experiments of Erlanger and of others described in Chapter IV These experiments resulted in hemoconcentration and the pathologic features characteristic of shock were noted in the viscera by the authors. It has been suggested (see Chapter IV) that hyperactivity of the sympatho-adrenal system is a cause for shock and the production of maximal arterial constriction by adrenalin has been cited as an example However it is unsafe to conclude that because shock can be produced experimentally through a certain agency, all instances of shock are due to that agency

Deficiency of cardiac function from various causes results directly in a diminution of the *Volume Flow* and causes death from deficient delivery of oxygen to the tissues. Examples of this are seen in valvular lesions with decompensation and in myocardial failure from any cause It is well known that coronary occlusion, if not immediately fatal, will produce the complete clinical syndrome of shock The mechanism of this effect is perfectly intelligible when its relationship to *Tissue Anoxia* is recognized

Many of the causes for *Tissue Anoxia* have already been considered Let it be emphasized that the circulatory effects of anoxia will be the same, regardless of whether it originates from

inadequate internal respiration or from asphyxia Several poisons such as hydrocyanic acid, carbon monoxide or morphine, interfere with the delivery of oxygen to the tissues and their effect is due primarily to systemic lack of oxygen This produces endothelial damage and thereby initiates the same sequence of disturbance as do other noxious agents

The visceral appearances when death is rapid differ somewhat from those seen when it is somewhat delayed, but the differences are distributional rather than qualitative In the former the process is rapid, sometimes almost instantaneous, selective distribution of circulation, favoring vital organs, has not had time to occur Hence cyanosis of the skin surfaces, as well as of visceral areas, is commonly seen Shock is more gradual in its development and, as circulatory deficiency begins, the blood supply to the periphery is restricted The skin becomes cold and the arteries leading to the limbs are almost pulseless Correspondingly the visceral congestion in this state is more intense, and the cutaneous surfaces are pale rather than cyanotic

Anoxia not only affects the capillaries directly as has been set forth, it may also produce indirect effects by disturbing the metabolism in the tissues Examples of this are seen in the experiments in which shock was produced by obstructing the circulation to the limbs No systemic effects were seen until the obstruction was removed, after which shock developed rapidly The authors believed that lack of oxygen in the limbs caused abnormal products of metabolism which, when released into the systemic circulation, caused shock to develop The same mechanism may be a factor when prolonged arterial constriction has been produced by adrenalin

The instances cited indicated that the sequence of effects which constitute the vicious circle of shock, may be initiated at various points in the circle In each instance the circulatory effect was similar and indicated the reciprocal relationship of *Capillary Atony* and *Tissue Anoxia*

THE MECHANICS OF DEATH

The author invites thoughtful consideration of the mechanism by which vital functions finally cease in death from so-called natural causes. Haldane's statement that the immediate cause of death is practically always anoxemia, is endorsed by physiologists This is the condition which "stops the machinery and

wrecks the machine" The primary cause may have been dise
of infectious, metabolic, toxic or neoplastic origin yet eit
respiratory or circulatory failure develops in the final stage of
Consequently anoxia is introduced as a terminal factor, and
causes capillary atony as effectively as if endothelial injury h
been the primary event The effects upon the systemic circulat
will be qualitatively similar, regardless of the cause for the cap
lary atony This consideration may explain the clinical, b
chemical and morphologic similarities, whether death con
rapidly by direct injury to endothelium or whether indirectly
gradually developing anoxemia incident to diverse processes
disease

The clinical picture which develops, as the moribund st
approaches, replaces significantly the previous symptoms Co
gestion and edema of the lungs are danger signals indicating
gravity of the condition Thirst, nausea, vomiting rapid shall
respirations and increased pulse rate suppression of urine, loss
tissue turgor, clammy skin and cold perspiration are characteris
signs. Finally the "Hippocratic facies," the carpology, the clouc
mental state and the falling blood pressure indicate the imminer
of death

These clinical signs are accompanied by equally signific
chemical and physiologic disturbances. In the moribund st
from various causes the blood becomes dark, its oxygen cont
is low and its clotting is delayed the urea, creatinin and no
protein nitrogen increase the distribution of electrolytes and fl
is disturbed, the sodium and chlorides decrease while the potass
content rises the alkaline reserve and the metabolism decline

The visceral appearances when shock has developed rapi
after trauma burns or intoxication differ only in degree fr
those seen when death has come more gradually from sunc
natural causes. In the former there is acute capillo-venous co
gestion of the lungs and of the serosæ and mucosæ, there
petechial hemorrhages in these structures in the brain and me
inges and in parenchymatous organs, marked edema of the lu
and mucosæ and blood tinged effusions in serous cavities Wh
anoxemia occurs as the terminal event in diverse types of illne
the lungs are less congested and edematous their weight is not
markedly increased petechiæ are not present, and serous effusio
are not marked nor are they tinged with blood.

It is both remarkable and significant that the clinical featur
the functional disturbances and the visceral changes are alm

identical whether death has occurred rapidly by shock or whether more gradually after some grave illness It appears that the effects of anoxia supply the explanation for these resemblances, careful scrutiny reveals no other factor in common, and it has been shown that anoxia alone will duplicate the syndrome of shock or of the moribund state from various diseases

The enigma of shock has baffled physicians and investigators in their attempts to elucidate its nature and origin The occurrence of circulatory failure and death, when no vital organs had been injured, was inexplicable All natural phenomena have been mysterious until explained or understood, then they become logical and relatively simple It now appears that shock is merely the approach of death by its usual mechanism—the reciprocal effects of *Tissue Anoxia* and *Capillary Atony* Comprehension of this relationship dispels the mystery from this phenomenon The *Vicious Circle* of shock may appropriately be considered as the *Cycle of Death*

TOXEMIA VS. ANOXEMIA

A clinical condition which develops in the late stages of serious illness, is often interpreted as "toxemia" The rapid feeble pulse, the "Hippocratic facies," the thirst, nausea and vomiting, the depressed renal function, the increased nitrogen content of the blood, the restlessness, anxiety, clouded mental state and final torpor or semi-comatose insensitivity, are frequently attributed to the effects of some toxic substance Likewise the circulatory collapse is often assigned to myocardial degeneration caused by the same hypothetic toxin The parenchymatous changes seen *post mortem* in the liver, kidneys and myocardium, are usually assigned to the same cause

In considering the validity of this interpretation, let it be emphasized that simple anoxemia from any cause will duplicate both the clinical features and the parenchymatous degenerative changes as described Attempts to demonstrate a toxic substance in the blood have failed, almost without exception, in each of the conditions mentioned The pathologic physiology of burns furnishes an excellent example Clinically the evidences of "toxemia" are unmistakable, and the opinion that some toxic substance results from thermal injuries has been held by many Yet most painstaking efforts have failed to demonstrate such a substance

The vascular effects of cytoplasmic substance (Chapters I, IV

and VII) discharged from cells in response to injury explain the disturbances formerly attributed to some hypothetic "toxin"

The conception of toxemia in diverse conditions of disease appears to originate by a process of inference or deduction Many agents such as poisons, venoms histamine, bacterial toxins, peptone and the like if injected into the blood produce the clinical syndrome described and interpreted as intoxication Therefore when that syndrome develops after trauma, burns and other catastrophes it has been ascribed to toxemia.

In the final analysis the validity of this view depends on the definition of terms. If all agents which produce relaxation and permeability of capillaries shall be regarded as toxins, then the conception of toxemia is substantiated However that definition would include normal metabolites, cytoplasmic substances and lack of oxygen as toxins.

Capillary atony is a terminal factor in grave diseases of diverse kinds. It produces clinical manifestations usually ascribed to "intoxication." So far as the actual mechanism is concerned many phenomena called *toxic* are essentially *anoxic*

IN CONCLUSION

To this writer it does not appear that the proposed explanations for shock are fundamentally incompatible or that the barriers to agreement are insuperable It is perhaps natural that those who deal practically with battle wounds, accidental injuries and the aftermath of extensive surgical procedures, should regard traumatic shock as an entity distinct from other phenomena of disease When a healthy vigorous person suffers extensive trauma, there is something both dramatic and mysterious in the progressive failure of circulation and the inexorable approach of death no vital organ having been damaged Proximity to this manifestation magnifies it in the view of surgeons, many of whom appear to regard it as a condition *sui generis* not related to the same manifestation originating under other conditions.

Observers from a more detached viewpoint may gain a perspective not apparent to the surgeon. They see the same syndrome accompanied by identical physiologic and biochemical disturbances and by identical pathologic changes in the viscera in grave conditions of disease in which no traumatic injury is present and no blood nor fluid has been lost locally They see shock in a broader perspective and recognize that its development after injuries is only one of the many conditions of its occurrence.

A surgeon states that surgical shock has not one but many causes: the anesthetic, the local loss of blood and fluid, anoxemia, emotional influences as fear or pain, vascular reflexes, loss of fluid by vomiting and otherwise, infection, intoxication and the debilitating effects of the disease which made operative procedures necessary, that the relative importance of these factors varies in each case and that they operate in varying combinations in different cases

An observer with the broader outlook not only admits all these observations, he reiterates them with emphasis So far, the agreement is perfect and no cause for argument exists But have *all* the etiologic factors been enumerated and considered? Would it not be appropriate to extend our horizons sufficiently to recognize a fundamental kinship between the mechanism of surgical shock and of that originating in other conditions, and to admit that toxic products of protein cleavage, endogenous in origin, should be listed among the factors which may initiate shock?

It appears that such an admission is harmonious with an enormous mass of physiologic, experimental and clinical data and that no invalidating evidence has been shown Such an admission would abolish at once the chief controversial aspects of the subject and would thereby contribute to the progress of medical science Fundamental principles having been agreed upon, investigations on other features of shock could go forward in an atmosphere cleared of controversial discussions

PART II

The Prevention, Recognition and Management of Shock

FOREWORD

As is our pathology, so is our practice —OSLER.

IT would be presumptuous for one who is neither surgeon nor internist to write upon technical surgical procedures or to advise concerning the medical management of the sick. Ability to apply to the individual case, remedial measures and principles derived from all fields of medical science is important in the art of medicine. A pathologist will not proffer instruction in that art.

The effectiveness of treatment depends essentially upon its relationship to pathogenesis. Hence those conversant with the various factors in the etiology of a condition, are competent to appraise methods for counteracting it and to compare with that appraisal the recorded experiences of practitioners.

Those who pilot vessels through dangerous waters are guided by charts showing details of reefs, shoals, channels and currents. In early days, the charts were drawn by navigators who had learned the channels of safety by experiences on the reefs and shoals. In modern times, such charts are prepared by cartographers who have surveyed and plotted with minute care each detail of that coastal area. The cartographer may never have piloted precious vessels through the channels shown on his maps, and the navigators seldom inquire whether he had done so.

New technical methods for the early recognition of shock and a new mode of clinical attack, have developed recently. Methods for preparing, storing and using plasma, serum and blood substitutes have opened a new epoch in the treatment of shock. An analysis of the relationship of these items to the mechanisms involved should be useful as a guide in practical management. The author believes that an evaulation of remedial measures as related to the vascular dynamics of shock will be welcomed both by surgeons and by internists.

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CHAPTER XVIII

THE PREVENTION OF SHOCK

The best treatment for shock is prevention —CRILE.

THE prevention of shock requires first, a thorough comprehension of the various conditions under which its development may be expected, second, an understanding of its mechanism, and third, the application of practical measures for counteracting or eliminating the factors in that mechanism The various factors entailed, the mode of their action and the conditions of their occurrence have already been considered Attention is now invited to the application of practical measures for the prevention of shock

SURGICAL SHOCK

As stated previously, the circulatory failure which develops after surgical operations results from the combined effects of the disease which necessitated the operation, the anesthetic, the absorption of substances from damaged tissues, hemorrhage and loss of fluid in the area of surgery or trauma The effect of fear, pain, and other emotional responses should be added to the group of factors mentioned

The condition of disease which necessitates surgical intervenion, is taken into thoughtful consideration in the choice of procedure whether palliative or operative To estimate the degree of the operative risk requires an accurate evaluation of the patient's physiologic reserve It requires a high type of judgment, based upon wide experience and observation, to decide whether operative procedures, in a given case, entail greater hazards or greater probability of benefit These considerations vary in each individual case, hence a theoretic discussion of them is not profitable

Anesthesia.—The contributory effects of anesthesia are indisputable It has been shown that about 10 times as much histamine is required to produce shock in unanesthetized animals as in those under ether anesthesia General anesthesia usually is not sufficient to cause circulatory failure in a normal healthy person or animal, but its contributory effect is great and it may narrow to a dangerous degree, the margin of safety A person who has sustained severe physical injury, but without evidence of circu-

latory deficiency may develop shock when anesthetized for operation The same statement applies to those whose present conditions of disease make them "poor surgical risks."

Both anesthetists and surgeons recognize that the choice and use of anesthetic agents must be adapted both to the individual patient and to the contemplated operation The debilitating effects of disease may render hazardous any form of general anesthesia A weakened but adequately compensated circulation may quickly show signs of decompensation under anesthesia alone or when operative procedures are begun, this is true either in cases of cardiac impairment or when peripheral circulatory deficiency threatens or may be feared It is not within the province of this discussion to give instruction in adapting the anesthetic to the conditions of the individual case, but rather to consider the properties of anesthetic agents as related to the mechanism of shock

Cattell stated that ether causes a decrease in cardiac output which produces a decline in blood pressure, both in normal and in shocked animals. Barbour and others have shown that ether causes hemoconcentration which may range from 10 to 15 per cent. This was confirmed by Bourne who noted that general anesthesia tends to disturb the water balance to lower the alkaline reserve to decrease the pH and to diminish the volume of urine excreted He stated that all inhalation anesthesia causes some depression of renal function His survey of the subject indicated the choice of 3 procedures regional anesthesia, *i e*, local or spinal general anesthesia with nitrous oxide or cyclopropane, or a combination of the two methods. He regarded all other forms of anesthesia as obsolescent because of their untoward effects.

When one considers the disturbances of physiology mentioned above, he understands why general anesthesia increases dangerously the effects of conditions which tend toward shock The experiences of military surgeons in the previous war indicated that nitrous oxide anesthesia was less apt to precipitate shock in wounded soldiers than was ether or chloroform Dale found that nitrous oxide plus oxygen contributed less than ether anesthesia to shock by histamine in cats. That principle has been verified in the present world catastrophe in treating air raid casualties, it is reported (Grant) that the inhalation of nitrous oxide combined with oxygen contributes to shock less than other agents do

Yet nitrous oxide even combined with oxygen, is not free from danger Courville reported detailed studies on 9 fatalities resulting

under such conditions These included necropsy examinations and a critical study of cerebral tissues The changes found included congestion, edema and hemorrhages in the meninges and brain, and severe degeneration, extensive necrosis, sclerosis and calcification, these involved chiefly the cerebral cortex and the lenticular nucleus Postmortem data on other organs were not given in detail, "bronchopneumonia," visceral congestion and degeneration of liver and kidneys were mentioned His studies led to the conclusion that both the clinical symptoms and the pathologic findings resulted from asphyxia and not from toxic effects of the gas itself

Spinal anesthesia obviates many of the disadvantages which attend general anesthesia, yet it has the unfavorable effect of lowering the blood pressure The mechanism of this appears to differ from that produced by ether, which of itself effects endothelial permeability, facilitates the development of edema (Barbour), causes hemoconcentration and lowers the blood volume Decreased arterial tension from spinal anesthesia is not accompanied by concentration of the blood nor by reduced blood volume Apparently it is caused by arterial dilatation which may be counteracted by vasoconstrictive drugs such as neosynephrine (Bourne, Silvers) and produces less serious harm than does endothelial permeability

Lemmon recently devised a technique by which the degree of spinal anesthesia may be kept under control during the operation The spinal needle is inserted and kept in place until the operation is finished It is connected by rubber tubing to a 10 cc Luer syringe containing novocain, procaine or other anesthetic agent in solution By opening a cock, then pressing or withdrawing the piston of the syringe, varying amounts of the anesthetic agent may be given or withdrawn from the spinal canal as required By this means the anesthetic is administered "fractionally," *i e*, no more is given at one time than is required to block sensory impulses When the operation is finished, the anesthetic solution may be drained from the spinal canal and replaced by saline solution This minimizes the circulatory and systemic effects of the anesthetic and reduces the danger of shock The technique requires a special needle and an operating table constructed with an open space to accommodate the needle and its connections Surgeons who have used this technique for spinal anesthesia, speak enthusiastically concerning its advantages

Blalock endorses spinal anesthesia for operations below the

umbilicus, if administered by a skilled anesthetist. In discussing the advantages and dangers of different forms of anesthesia he gives well placed emphasis to the necessity for avoiding anoxia. This item appears to be the most potent element of danger presented by many anesthetic agents Since anoxia is one of the major factors in the mechanism of shock one cannot over-emphasize the need for avoiding it.

Various chemical combinations of barbituric acid have been proposed as less dangerous than ether when shock is feared The experiments of Seeley, Essex and Mann indicated that shock was induced in dogs less easily under amytal anesthesia than under ether On the other hand in an extensive comparison of the effects of hemorrhage in unanesthetized dogs and in those given amytal (see Chapter IX) we found that the latter succumbed to about one-half the loss of blood required to cause death in the former The barbiturates facilitate the development of shock by their deleterious effects on endothelium (Goodman and Gillman) Bourne stated that 'evipal' and other barbiturates in therapeutic doses produce relatively severe anoxia and that 'avertin' or tribromethanol has a similar action

Inhalation anesthesia is accompanied by deleterious effects on parenchymal cells. This statement applies to the degenerative changes found in the brain kidneys and liver after deep anesthesia with chloroform, ether or nitrous oxide. The effects of the latter appear to result chiefly from anoxia (*vide supra*) and those of the others are due at least in part to the same Goldschmidt Ravdin and Lucké investigated this feature and reported that an adequate supply of oxygen, combined with general anesthesia, protects the liver against such damage Coleman compared the effects of five anesthetic agents upon the liver Ranked in descending order of severity these were avertin nitrous oxide and ether spinal nitrous oxide plus oxygen and local anesthesia.

Several British surgeons have found local anesthesia most satisfactory for operations after battle wounds and air raid casualties. Clarke and Kessel reported that local anesthesia diminishes the incidence and the degree of shock as compared with similar operations done under general anesthesia. Dodd stated that after spinal or local anesthesia, the postoperative progress is smoother, the mortality lower and the final results better It is obvious that local anesthesia will cause less systemic effect than will general anesthesia. Under similar conditions of use the former will contribute less to anoxia and to circulatory

failure than will the latter. This principle would seem to apply also to spinal anesthesia when expertly administered

Morphine is given to allay pain after operations, trauma or burns, and its usefulness for this purpose is unquestionable Morphine also allays apprehension and other emotional reactions and should be given sufficiently to secure quiet and comfort But its effects beyond this point are to be avoided

Morphine depresses the activity of the center which governs respiration, this retards the respiratory rate, reduces the supply of oxygen to the tissues and lowers metabolic activity It is emphasized again that anoxia is a major factor in the mechanism of shock The use of morphine beyond the amount necessary to allay pain, is contraindicated because of its tendency to produce anoxia

At one time it was the vogue to give CO_2 by inhalation in attempts to prevent acapnia Apparatus which allowed the patient to rebreathe his own exhalations was devised, advocated and used extensively, even after it was shown that acapnia is not a cause for shock The inhalation of CO_2 accelerates the development of experimental shock in animals (Cannon, Coonse and others) Many surgeons found that their results under anesthesia with rebreathing were not so satisfactory as before that innovation was adopted There is no apparent physiologic reason for its use in surgical anesthesia The logical procedure is to combine oxygen with the anesthetic agent in order to counteract the tendency toward anoxia

Let it be emphasized that, regardless of what anesthesia is used, its contributory effect will be directly proportional to its amount and duration The surgeon who desires to minimize this, will do so by reducing the time of the operation to the minimum which is consistent with careful and effective operative technique

Experienced surgeons reduce to the utmost the effects of absorption by avoiding all unnecessary trauma during operations They use sharp instruments because a dull knife damages the tissues far more than does one which is keenly sharpened They reduce the application of clamps and hemostats so far as possible because the aggregate amount of tissues crushed by them may be considerable When ligatures are applied, they remember that all the tissue distal to the ligature must die from lack of blood This necrotic tissue will be absorbed into the system, and its effects are added to those of other factors Manipulation of the viscera is done gently and is not done unnecessarily It is recalled that an

effective method for producing shock experimentally is to manipulate forcibly the abdominal viscera of anesthetized animals. All unnecessary sponging or rubbing of serous surfaces and of exposed tissues is avoided

Hemorrhage and Loss of Fluid.—To stress the importance of hemorrhage as a contributory factor is to emphasize the obvious. Massive hemorrhage will cause death when the oxygen-carrying capacity of the blood is reduced below the minimum of physiologic limits. Medical experience has shown that a healthy unanesthetized person or animal will survive repeated uncomplicated hemorrhages which gradually reduce the erythrocytes and hemoglobin to 30 per cent of the normal or even lower A sudden hemorrhage produces more serious effects than the gradual loss of the same volume of blood

But minor degrees of hemorrhage occurring coincidental with disease anesthesia, trauma or surgery may produce serious or fatal results Cannon s experiences in the treatment of shock at casualty clearing stations led him to emphasize repeatedly that shocked patients and those whose injury is such that shock is feared are highly sensitive to hemorrhage "A small loss of blood wholly without permanent effect under ordinary circumstances, may cause a calamitous fall of pressure Special care should be exercised during operation on shock cases not to lose a drop more blood than actually must be lost And all tissues should be handled with extreme gentleness

The contributory effect of hemorrhage was exemplified in some of the experimental work on shock Roome Keith and Phemister found in dogs under anesthesia that the loss of 58.6 per cent of the estimated volume of blood would cause death if withdrawn within an hour If withdrawn more slowly 70 per cent of the total volume produced the same effect They found that dogs similarly anesthetized died from much smaller hemorrhages if subjected to trauma or intestinal manipulation The average amount of blood necessary to cause death, when combined with trauma to an extremity was 24 per cent, when combined with intestinal manipulation the average amount was 18 per cent

Loss of fluid into the tissues, or by vomiting purging or perspiration is not so serious a condition so long as the mechanism for maintaining water balance is undisturbed Moderate losses of blood or fluid are compensated readily by absorption of fluid from the tissues. But that mechanism is thrown out of function by hyperpermeability of endothelium In that condition, the

mechanism of absorption is deranged and losses of blood and/or fluid become more serious

Any loss of blood or fluid is of consequence when circulatory deficiency threatens, and its importance is directly proportional to the volume of blood and/or fluid lost

Surgeons are well advised in avoiding all direct losses of blood, also unnecessary trauma which may cause leakage of plasma into the tissues Degrees of these which would cause no ill effects in a normal person, may be of serious consequence when combined with the effects of disease, anesthesia and of absorption from traumatized areas Gatch and Little determined the amounts of blood absorbed on sponges, towels and pads during various types of ordinary operations Their figures indicated that the usual loss of blood is much larger than the operators realize. They advised adequate transfusions to replace such losses.

The oxygen-carrying capacity of anemic blood is less than that of normal blood, proportional to the degree of anemia Hence anoxia develops more readily in those whose red cells and hemoglobin are below normal The operative risk may be reduced by giving transfusions preparatory for major surgical procedures in such cases

The practice of giving saline solution intravenously before the patient leaves the operating room is logical In many surgical clinics it is standard practice to give saline combined with 5 per cent glucose solution The rationale for this is not based upon physiologic principles, and it is questionable whether the combination is more effective than saline solution alone In shock the blood sugar already is *above* normal, the depression of metabolic activities is not due to hypoglycemia *Glucose diffuses readily through endothelium, hence the increased osmotic pressure secured by introducing it, is very transient* Starling found that the increased osmotic pressure which resulted from an injection of glucose, had subsided within ten minutes Such fleeting effects as this would not delay the development of shock nor would they aid materially in reducing its degree The administration of glucose solution seems to be a routine practiced by most surgeons, apparently it does no harm, consequently it is not to be censured

A transfusion of blood, plasma or serum is given as a preventive measure if conditions are such that shock is probable The volume of blood or plasma which may prevent shock is much smaller than that necessary to combat circulatory deficiency when it has developed

Psychologic Factors.—Experienced surgeons agree that the psychologic attitude of the patient is a factor of importance Many refuse to operate except in emergencies when apprehension and fear of the operation are great. Patients whose dread of the ordeal is excessive are said to be poor risks. They may die while the anesthesia is being given and they develop shock more readily than patients whose disease is similar but whose mental state is one of confidence

A similar phenomenon is observed in animals. Many experimenters have noted that dogs which show great fright and which struggle strenuously when given ether may die before or during operative procedures This occurs so frequently that many workers have adopted a routine for minimizing this danger Some give a sedative or narcotic before giving the general anesthesia others avoid fright and struggle by placing the animal in a closed cabinet and introducing a sponge soaked with ether Many surgeons give a sedative which tends to reduce the apprehensive state of the patient prior to anesthesia.

The exact mechanism by which psychologic influences affect the circulation is not known. But the avoidance of that hazard is a precaution well supported by experience

INJURIES, IMMEDIATE TREATMENT

Experiences gained during the early years of World War I, later became standard practice in caring for wounded men These are summarized in the final chapter of Cannon's monograph, *Traumatic Shock* The principles set forth were based upon experiences with great numbers of all forms, degrees and complications of casualties. They are equally applicable to injuries incurred in civil life

Detailed instructions[1] were issued to medical officers for the care of the wounded the prevention of shock was a major consideration The instructions embodied the following measures

Hemorrhage was controlled by ligature of the bleeding vessels, by packing deep wounds with gauze and by applying snug bandages to provide moderate pressure Tourniquets were applied only when other methods had failed

Cold was combated by applying blankets as soon as possible, by supplying artificial heat from a primus stove hot bricks or water bottles, and by the use of a warming chamber Hot drinks were given by routine it was urged that all wounded men need fluid by mouth.

[1] Official History of the War Medical Services, Surg. I p. 73 London H M Stationery Office 1922.

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[1] Official History of the War Medical Services, Surg I p. 73 London, H M Stationers Office 1922

Pain was counteracted by giving morphine early and as often as needed Emphasis was laid upon immediate and efficient splinting of injured limbs and upon care and gentleness in the lifting and transportation of the wounded

Tincture of iodine was applied locally to fresh wounds Infection was combated by *early* surgical treatment of wounds, by careful dressings and by rapid evacuation to hospitals

Reports on the immediate treatment of battle casualties and of those injured in air-raids in the present conflict indicate that the same general measures are applicable An official statement issued by the National Research Council[1] endorses the principles set forth above and gives other important instructions for the prevention of infections in wounds and burns Many of the items pertain to surgical asepsis, disposal of contaminated material and to standard prophylactic measures

"Recent experiences have demonstrated beyond doubt the value of the application of crystalline sulfanilamide to wounds which are awaiting débridement This should be applied liberally to all wounds as soon as practicable after they have been incurred It is recommended that every wounded man be given 1 0 gm of sulfanilamide every four hours for 6 doses until definite surgical treatment has been accomplished

"As soon as possible after the injury the wound should be débrided Major blood vessels and nerves should not be sacrificed All necrotic skin, fascia and muscle must be excised The wound should then be thoroughly irrigated with sterile physiologic solution of sodium chloride After this, not more than 5 gm of crystalline sulfanilamide shall be placed in any one wound or 10 gm in all wounds of a single patient After débridement, irrigation and the local use of sulfanilamide, the area should be covered with petrolatum gauze and carefully dressed

"*Institute shock therapy at the earliest possible moment and continue it up to the time of operation It consists essentially of (1) giving morphine, (2) keeping the patient warm and (3) giving blood plasma*" (Italics mine)

This official statement also contains detailed concise instructions concerning surgical technique, operative and postoperative care, drugs, dressings and equipment

Control of Hemorrhage.—The laity have been informed from various sources, that a tourniquet applied proximal to a wound it the proper way to control hemorrhage This formerly was endorsed in treatises on surgery and in manuals on first aid Tourniquets often were applied as first aid to wounded men and were still in place when they arrived at casualty stations several hours later

[1] National Research Council Prevention of infection in wounds and burns Prepared under the auspices of the Committee on Chemotherapeutic and Other Agents and the Committee on Surgery of the Division of Medical Sciences War Med , 1942 (May) 2, 488–496

The removal of these was followed not infrequently by the development of shock. Subsequently it was shown (Wilson and Roome, Allen) that constriction of the limbs of animals by tourniquets caused shock when released. On the basis of experiences, Wallace and Fraser caused the following instructions to be issued

Bleeding is to be arrested by pressure upon, or ligature of the bleeding point itself and not by constriction of the limb above or by tying the artery on the proximal side of the injury The systematic use of the elastic tourniquet should be limited, and its use, apart from during an operation, should be restricted to those cases in which a limb is completely smashed or blown away or as a temporary measure while a patient is being carried to a regimental aid post If the medical officer finds that a tourniquet has been already applied, it is his duty to remove it at once and to examine the limb, so as to ascertain whether there is actually hemorrhage and, if so to take measures for its arrest.

The suggestion was offered

that if a limb has been so badly mangled that it cannot be saved a tourniquet should be set close above the traumatized tissues and left in place *until after amputation* The amputation should be performed proximal to the tourniquet. Thus, throughout the period of transportation and preparation for removal of the limb, the body is protected against toxic material which is present in the torn and smashed tissues and is likely to be absorbed "

Hemorrhage usually may be stopped by applying pressure on the wound A compress may be bound to the wound, using care not to constrict the arterial circulation by a bandage too tightly applied

If bones have been broken, a temporary splint is applied outside the clothing before lifting the person onto a litter or attempting any form of transportation If no splints are at hand a broom handle walking stick or piece of lumber may be serviceable This precaution tends to prevent further hemorrhage, also it lessens the injury of soft tissues by the ends of the fractured bone

When the patient arrives at the accident ward the clothing is removed preferably by cutting He is then examined carefully both as to the nature and extent of the injuries and as to the condition of the circulation If injuries are severe and obviously require immediate surgical attention it is advised (Grant) to take him at once to the operating room before removing the clothing then if hemorrhage begins, under preparation and examination it can be controlled promptly If the condition of the circulation is not satisfactory it is advised to postpone operative procedures, other than necessary hemostasis, and to institute restorative measures before giving surgical care to wounds The

patient is placed in a warmed bed, covered with an electric cradle, given hot drinks and sedatives if required, and carefully watched.

If the patient is severely wounded, pale, almost pulseless and has rapid shallow or gasping respirations, he is placed at once on a bed elevated at the foot and a transfusion of blood, serum or plasma, is begun at once. In cases of severe hemorrhage, whole blood is given rather than plasma or serum. Do not waste time in making repeated attempts to insert a needle into veins which are collapsed and hard to enter, open the skin and insert a needle or cannula. "Many patients will do well on no more than rest and warmth and morphia, and are soon ready to undergo operation."

Heat.—Loss of body heat contributes greatly to the development of shock. It is prevented by wrapping well with blankets. As many layers of blanket are required on the cot or stretcher as covering the patient. A cage or "cradle," covered with sheeting or with blanket material and fitted with bulbs or other electric heating units, is convenient for supplying warmth. In the previous war, blankets were draped over the patient and a kerosene lamp placed under the cot. Hot drinks are highly effective in combating loss of heat. Clothing wet with perspiration or otherwise, should be removed at the earliest possible moment. "The clinical improvement seen when a wounded man, cold and shocked, is merely put to bed and warmed is often astonishing. The pulse, absent at the wrist, may return in good volume and within an hour the blood pressure may rise to a satisfactory level" (Cannon).

The suggestions concerning heat are applicable when an injured person, perhaps cold, wet and suffering from exposure, is brought in. Often they are useful in the absence of exposure, but the same principles are sometimes followed injudiciously after major surgical procedures not related to wounds or accidental injuries.

Precautions to prevent chilling are regularly employed both during and following operation. The operating room often is kept at a temperature above that of other rooms, the patient is well covered with blankets and heat is often applied artificially. Few surgeons realize that these measures if overdone, defeat their own purpose and that judgment is required in their application. A standard routine of keeping patients warm may be dangerously overdone by zealous attendants. The direct application of even moderate heat causes dilatation of skin capillaries. This is a factor of real importance when circulatory deficiency is present or is feared. It increases the total volume capacity of the vascular system and accentuates the effects of decreased blood volume which is present regularly in shock.

Furthermore, if heating is mildly overdone it results in perspiration Sweat is salt solution lost by the system. It can be replaced readily under normal conditions but it lessens the amount of fluid available to preserve the blood at a standard level of dilution The development of shock may be accelerated by excessive application of heat.

Allen found that rats kept at a low temperature developed shock more slowly than those kept warm, under otherwise identical conditions of experimentation Blalock advises that patients should not be chilled, but that heat should be used with moderation and over-heating avoided "Patients with incipient or fully developed peripheral circulatory failure should be kept warm but it should be borne in mind that excessive heat may exert as severe ill effects as excessive cold"

Summary —Surgeons have been able to reduce to a minimum the occurrence of shock following operative procedures They report that ominous circulatory deficiency of this type rarely occurs in modern surgical practice and they attribute this achievement to precautions taken for the prevention of shock

The first of these is pre-operative The nutrition and general condition of health are given days, or perhaps weeks of attention for the purpose of raising so far as possible the physiologic reserve A period of hospitalization may be advisable during which adequate diet food and rest may improve the physical status, and minor ailments may be corrected or relieved Those who are anemic are treated appropriately, often by transfusion of blood It is recognized that the better the physical condition the smoother will be the postoperative period.

During the operation the traumatization of tissue the loss of blood by hemorrhage, and the duration of the anesthesia are reduced to the absolute minimum When extensive or complicated procedures have been such that shock is feared, transfusions of blood of plasma or serum or saline solution given intravenously, maintain the circulation and reduce the danger of its subsequent deficiency These precautions usually are taken before the patient leaves the operating room

Those who have suffered wounds or accidental injury are handled as little as possible are transported without delay and as gently as may be after temporary splinting and hemostasis, and are treated with the prevention of shock as a purpose

These precautions have resulted in a decreased occurrence of shock after operations and after battle wounds and accidental injuries

CHAPTER XIX

PREVENTION OF ABSORPTION

No factor in the *prevention of shock* exceeds in magnitude of importance the *prevention of absorption* This statement has been considered thoughtfully and it is no exaggeration Absorption is both an initiating and a sustaining factor after battle wounds, accidental injuries, visceral perforations, burns, intestinal obstruction and severe regional infections The materials absorbed include cytoplasmic substance, which of itself causes capillary relaxation and endothelial permeability (Ebbecke, Lewis), products of autolysis of damaged tissues which have the same effects (Chapter VII), and products of bacterial growth The latter group of substances is of high importance in lacerated contaminated wounds, perforations of abdominal viscera and in infections of the tissues with gas bacilli or with other organisms

WARTIME CASUALTIES

Military surgeons divided wounds from projectiles and shell fragments into 3 main groups They classed as *avulsive* wounds those in which an area of flesh including subcutaneous tissue and muscle, had been torn out and carried away more or less completely *Perforating* wounds were those in which the projectile had gone completely through a limb or other part *Implunging* wounds were made by missiles which were almost spent, they penetrated into the tissues, carrying fragments of clothing with them, often leaving only a small opening in the skin at the point of entrance

The injury to soft tissues varied greatly but, excepting avulsive wounds, the damage was greater than was evident by external examination Frequently the wounded parts contained irregular cavities filled with blood, débris and foreign material The impact of projectiles traveling at high velocity was transmitted laterally and produced a zone of pulped or devitalized tissue surrounding the actual path of the projectile Often the external openings in the skin were obstructed by bits of muscle or by a large mass of relatively uninjured muscle, this resulted if a limb was flexed when wounded and later was placed in the extended position

(Fig 26) When a bone had been struck fragments of it were driven laterally and forward producing a crateriform wound of exit. *"Soft nosed" projectiles produced similar destructive effects.*

It was noted that a pointed bullet, striking "nose on" made a clean cut perforation on entering the tissues but if its velocity was 2000 feet per second or greater the wound of exit often showed an "explosive" effect even when no bone had been struck. This effect produced a large lacerated wound of exit. "Sometimes it is of great size and shows shreds of muscle and of tendons and fasciæ bound together by blood clot and protruding from an irregular crateriform opening in the skin" Bullets often break apart

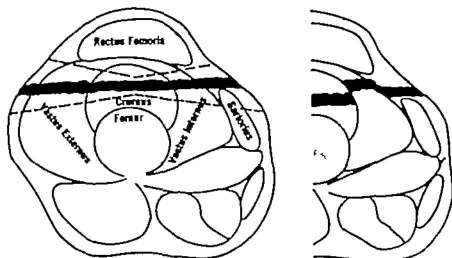


FIG. 26 —Diagram of a perforating bullet wound of the thigh. The track of the projectile may be closed by a shift in the position of the muscle. (From Med. Dept. of the U.S. Army in the World War v XI Surgery p. 301 Washington, Govt Printing Office, 1927)

within the tissues adding to the destructive effect and leaving fragments of the casing scattered at some distance from the path of the larger pieces. This happened especially after a bullet had richocheted or had struck bone the frequency of this effect led to the suspicion that the enemy was using explosive bullets.

It was noted that conditions which favored absorption were followed by more severe after-effects Widely open wounds in which flesh had been cut away were less severe in their after effects than the deeply penetrating wounds which communicated with the surface by only a small opening Multiple small superficial wounds as from shell fragments, appeared trivial in themselves but collectively they represented extensive tissue injury

and multiple foci of infection Such injuries were often followed by the development of shock [1]

Débridement.—At the outset of World War I, the types of wounds described were treated conservatively by incision, removal of fragments, and drainage The mortality from shock and from subsequent infections was disproportionate to the apparent gravity of the injuries French surgeons soon developed the more radical and effective operative technique of *débridement* This resulted in a decrease in the degree and incidence of shock and in a lower mortality from wounds The procedure was adopted soon by the surgeons of the Allied Armies, it was described by Poole as follows

"The skin incision, when possible, should be made parallel to the long axis of the limb This permits wide exposure of the underlying tissues and renders subsequent suture less difficult A transverse incision should rarely be employed In the case of a deep transverse perforating wound it is better to make 2 longitudinal incisions and work inward from each rather than to make a transverse incision with division or excision of considerable muscle tissue The tract is exposed in the middle of its course and débridement is carried out from this region in both directions The skin wounds of entrance and exit are excised by small elliptical excisions and the wound edges approximated

"The operation itself consists in the free excision of all tissues with which the foreign body has come into contact and all devitalized tissue, except structures such as nerves, large vessels and bones, whose removal would interfere with the function of the part and cause permanent disability Free excision, however, does not mean ruthless, blind butchery of the parts, but rather, careful, intelligent dissection, with liberal removal of such parts as should be removed, and with equally scrupulous preservation of such parts as may be left with safety

"The wound itself, with all contused skin, is excised by removing an elongated ellipse of skin No healthy skin should be sacrificed on the sides of the ellipse, as it is important to conserve as much skin as possible in the transverse plane of the limb to facilitate suture This is especially important in the forearm There is no advantage in attempting a débridement through a short incision A deep débridement demands a long incision The skin incision must always be vertical to the skin surface, the tendency to bevel the incision should be avoided, as this interferes materially with satisfactory suture (Fig 27)

"All traumatized and devitalized muscle must be removed This demands excision for a distance of 0 5–1 cm on all sides of the tract The dissection is made parallel to the fibers of the muscle, a long, relatively narrow ellipse is removed so that the sides tend to fall together after the excision The dissection should be made by planes, muscles should be

[1] Medical History of the War, Surg I, Chapter II, H M Stationery Office, London, 1922

identified and the situation of nerves and large vessels should always be borne in mind

Careful hemostasis is necessary at all stages Sponging of blood should be done by pressure and not by rubbing, because the latter method may carry organisms from an infected to a clean part of the wound and may cause a small tract to be lost to view The foreign body should not be extracted until reached in the dissection otherwise the parts fall together and the tissues immediately beyond the body which often contain clothing may not be adequately excised When the excision is complete all exposed muscle must look healthy contract when pinced with forceps, and ooze when snipped with scissors otherwise its vitality has been diminished to such a degree as to favor gas bacillus infection

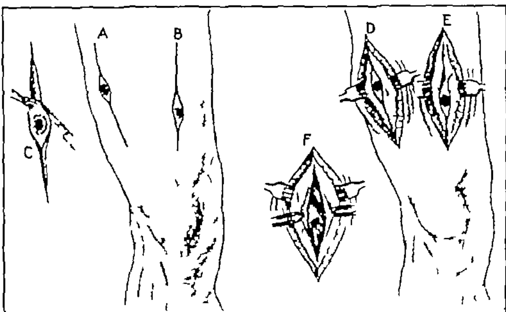


FIG. 27 —Illustrates successive stages in the débridement of a perforated wound of the thigh. (From Med. Dept. of the U.S. Army in the World War v XI Surgery p. 303)

This procedure left the wounded area free from foreign material fragments of bone and devitalized tissue and surrounded on all sides by clean viable tissue. The practice of débridement resulted in lower mortality, less extensive subsequent infection and earlier healing

The lapse of time before surgical treatment could be given was shown to be a highly important factor in the mortality percentage. Santy reported results on 79 cases in which the time between the reception of the wound and the surgical treatment was known accurately The results are shown in the table on p 234

The cases, as shown by the author's data, included wounds of similar extent and severity in each of the groups The progressive increase in mortality, when operation was delayed, indicates the necessity for early surgical treatment if death by shock or severe infection is to be avoided The first six hours after injury are called the *golden hours* because operative relief later is less effective

TABLE 4

Hours Intervening	*No of Cases*	*Mortality percentage*
1	10	10
2	9	11
3	8	12
4	11	33
5	9	36
6	12	41
8	8	75
9–10	12	75

Military surgeons noted that conditions which reduced absorption contributed to a favorable course and to recovery "As soon as possible there must be complete suppression of the trauma" (Wallace) This was accomplished by immediate rapid "guillotine" amputation of mangled limbs and by débridement of other wounds "The operation is commonly followed by a remarkable and maintained improvement so rapid and striking as to appear a direct sequel to the removal of the damaged limb " The experiences of the British, American and French military surgeons during the first world war were summarized by Cannon as follows

"The excellent results of prompt operation, performed on the severely wounded before the development of secondary shock, have been noted before this time The great French military surgeon Larrey, who followed Napoleon's campaign, laid down the dictum that crushing wounds of the extremities should be operated upon at once, for that treatment gives the only hope The figures given by Santy point to the action of some agency, which, as time passes, brings on the state of shock and seriously jeopardizes the chances of recovery The bearing of these observations on the toxic origin of secondary shock is obvious The crushed and lacerated tissues become not only a source of danger to the body from processes of death taking place in them, but they are most favorable sites for infection For both reasons, therefore, early clearing away of destroyed tissue, or débridement, is a prophylaxis against shock and other damaging conditions

"If secondary shock is already established when the patient, cold and depressed, is brought under surgical care, there is general agreement that simple measures, such as warmth, rest and fluids, should be applied in an attempt to improve his state before operative interference is begun "

The practice of dealing with extensive lacerated wounds by amputation or débridement has become standard A different type of injury has occurred from the bombing of cities during air raids over England Numerous victims were pinioned under débris for many hours before they could be rescued and given treatment. Such "crush injuries' presented features not often seen in previous wars. The compression of limbs under timbers and masonry even when unaccompanied by open wounds, hemor rhage or fractures was followed by secondary shock as indicated by hemoconcentration, low blood pressure and other signs. Several reports on crush injuries have appeared recently in British journals (Grant Mayon White Bywaters and others) These cases were given the usual treatment the blood volume was restored by transfusion of blood or of serum and the blood pressure was maintained at satisfactory levels yet many of them died These presented the features of shock with delayed death dis cussed under *Sublethal Shock* (pp 173–195)

The authors stated that the one feature common to these injuries was extensive necrosis of muscle Apparently the surgeons were not mindful of the danger presented by absorption from these areas the victims were treated as if with the hope of conserving the damaged limbs. Relief by amputation was attempted in one case the authors commented that 'early' amputation—done thirty-six hours after the rescue!—did not prevent a fatal outcome

It seems probable that one valuable lesson from experiences with crush injuries, will be that *early* amputation or débridement is as essential in these as in cases of badly mangled limbs.

BURNS

Davidson who laid the foundation for the modern treatment of burns, was convinced that absorption from burned areas, was the dominant factor in the systemic effects 'Of the various theories presented that which attributes the constitutional reaction to absorption of some toxic substance or substances from the burned area is most strongly supported by the available evidence " He sought means for combating the toxemia *by prevention* He attributed the toxemia to autolytic products of protein decomposition in the damaged tissue and discussed 4 possible means for counter acting this (1) by arresting the autolytic process (2) by removing the products of protein decomposition mechanically or by baths (3) by slowing the process of absorption by the use of vasocon

strictor drugs, (4) by causing a local coagulation of all devitalized tissue Since the practical and efficient application of the first three of these was difficult to accomplish, he adopted the suggestion of E C Mason that coagulation of the devitalized tissue by chemical agents would delay both the autolysis and the absorption of its products

Picric acid, previously used in the local treatment of burns, had the disadvantage of causing toxic effects by absorption of the drug when used in a concentration sufficient to cause coagulation of the tissue protein Experiments with boric acid did not produce satisfactory results The use of tannic acid (2 5 to 5 per cent solution) applied immediately and continuously to the burned area was followed by results far superior to those of any treatment previously used The reports of Davidson on this mode of treatment have made history

The routine finally adopted was to give the patient immediately by hypodermic injection a sufficient dose of morphine to allay pain The blebs were opened and the loose epidermis was trimmed off Then the burned areas were covered with sterile gauze pads held in place by bandages These were then saturated with a freshly made solution of tannic acid (the solution deteriorates on standing) The dressings were opened from time to time for inspection, any areas which remained red and moist were treated with tannic acid solution until oozing ceased and the surface became brown When all the burned surfaces had assumed a light brown color, the dressings were removed and the areas exposed to the air The parts were protected against mechanical injury by a frame or "cradle" draped with sterile linen

The purpose of the procedure was to coagulate *all* of the tissue devitalized by the burn With deep burns, this required the stronger solution of tannic acid applied for a longer time The subsequent dehydration of the coagulum was facilitated by moderate warmth from electric light bulbs under the cradle. It was found that the firm dehydrated coagulum was not a suitable medium for bacterial growth and that secondary infections were distinctly limited

The local treatment was accompanied by systemic measures for maintaining blood volume and fluid balance (p 269) This mode of treatment was found more effective than others previously used on burns of similar extent Burns of second degree healed completely without further treatment, in those of third degree, the coagulum contracted into a firm eschar under which healing

by granulation proceeded, and presently the eschar sloughed spontaneously

The advantages gained were a definite decrease in the degree of toxemia, the fever, hemoconcentration and non protein nitrogen of the blood were each relatively lower, the wounds were less painful, healed more rapidly, secondary infections were reduced and the resulting scar tissue was less in amount.

The coagulation of all the tissues injured by heat and the subsequent rapid dehydration of them, have become standard modern practice in hospitals and clinics Detailed instructions in these matters and in systemic treatment have been published recently by Harkins (175[16]) A few modifications of the technique for coagulation have been found highly effective Bettman reported that a 5 per cent solution of silver nitrate was more effective than tannic acid as a coagulant. Others have combined methyl violet or gentian violet with either tannic acid or silver nitrate solution for the purpose of inhibiting bacterial growth Wilson and associates have found the combination of 10 per cent silver nitrate solution with a 1 per cent solution of gentian violet most effective and have adopted this as a routine procedure

Recently Pickrell has reported the use of a coagulant combined with a sulfa compound to prevent infection Three per cent sulphadiazine in 8 per cent triethanolamine was sprayed onto the burned area with an atomizer Aseptic care was employed in the débridement of the loose epiderm and tissue. The mixture was applied every hour during the first day, at intervals of two hours on the second day three hours on the third day and once in four hours on the fourth. The author reported that this treatment produced a translucent pliable eschar and that subsequent infection was prevented or minimized In 115 cases, the healing was more rapid and the results more satisfactory than were obtained by methods of treatment previously used at the Johns Hopkins Hospital.

Burns so extensive as to prove fatal inevitably by other modes of treatment may recover if treated immediately by the methods described The advantages are due to several factors coagulation of the injured tissues retards both autolysis and absorption, hence toxemia and shock are reduced and the liver, brain and other parenchymal tissues are less effected by toxins and by anoxia. The coagulum does not distend with fluid, hence the local loss of plasma from the blood is reduced The dehydrated coagulum is not a suitable medium for bacterial growth hence the body is

protected both from infections and from products of saprophytic growth in the devitalized tissues

Systemic measures for combating the effects of burns are discussed in subsequent chapters (pp 265–271, 295–296)

INTESTINAL OBSTRUCTION

The effects of intestinal obstruction vary widely in severity depending on whether the obstruction is in the upper or lower bowel tract, whether it is complete or partial, and whether a loop of bowel is strangulated as by herniation, volvulus or adhesions The effects of strangulation are far more severe than those of simple obstruction The infarction of an area of bowel, as by an embolus in a mesenteric artery or by thrombosis of a mesenteric vein, produces as severe effects as does strangulation

In cases of strangulation or infarction of the upper bowel, the need for immediate surgery is imperative Every hour of delay increases the operative risk and the tendency toward shock It has been found that decompression of the distended bowel, by Wangensteen's method or by the Miller-Abbott tube, relieves the distress, lessens the vomiting and the manifestations of intoxication and facilitates the operative procedures For these reasons surgeons prefer to wait until decompression is accomplished rather than to attempt operations in the presence of greatly distended bowels Unless, as sometimes happens, the decompression actually relieves the obstruction, surgical intervention is not deferred long Absorption of toxic substances from the strangulated or infarcted bowel is not obviated by decompression, but proceeds apace The effects of this are progressive, hence delays beyond those necessary to reduce the operative risk by securing temporary improvement, are hazardous

The development of shock incident to intestinal strangulation or infarction is the product of several factors Chief among these is the absorption of injurious substances from the involved loop of bowel These include proteins and protein-split products from the devitalized mucosa, and substances resulting from bacterial growth in the mucosa and in the intestinal contents Persistent vomiting causes loss of fluid from the body, which loss is not readily restored because the mechanisms of fluid balance and of absorption are disturbed, resulting in dehydration of the tissues and in hemoconcentration Under these conditions, anesthesia and surgical procedures may readily precipitate the development of

shock For this reason many experienced surgeons employ local or spinal anesthesia and limit the operation to the minimum which will give relief It is not within the province of this discussion to advise surgeons concerning the choice of anesthetic agents or of operative procedures best suited to individual cases

The reason that strangulation or intestinal infarction is more serious than simple obstruction lies in the fact that areas of bowel wall are devitalized in the former while in the early stages of the latter mechanical hindrance to the passage of bowel contents is the chief feature. This fact makes necessary the early removal of the devitalized area before the effects of absorption cause irreversible systemic effects.

But unless simple obstruction of the bowel is managed intel ligently, the sequelæ may be of the same type as after strangula tion Simple obstruction causes distention of a segment of bowel above the point of obstruction If this distention is severe and continued it impairs the circulation in the minute vessels of the mucosa and submucosa, this leads to anoxia and to devitalization of the involved tissues. The effects of absorption from a distended devitalized area of bowel become like those of strangulation or infarction

The sequelæ mentioned may be prevented in large measure by the methods of Wangensteen or of Miller Abbott. Historically these methods represent an elaboration of the technique for duodenal drainage developed years ago (Einhorn, Rehfuss Lyon) A slender rubber tube, with suitable tip and lateral openings, is swallowed by the patient. After some hours this passes through the pylorus the duodenum the jejunum and into the ileum Gaseous distention is relieved and fluid contents of the bowel are aspirated by suction The clinical improvement resulting from successful intubation is described as spectacular Food may be given through a second tube passed to the stomach, and the residue of bowel contents evacuated by aspiration from the area above the obstruction

The advantages gained by these procedures are obvious Com fort is secured vomiting is relieved and the loss of fluid and of gastric secretions is prevented Nutrition is maintained and the absorption of toxic substances from bowel contents and from devitalized mucosa is prevented The pathologic effects of dis- tention upon the bowel wall are prevented and the imminent danger of shock is lessened The condition of the patient may be improved and such operativ[illegible]

to the case may be performed not as emergency measures but at a chosen time under controlled circumstances with minimized risk.

INFECTIONS

For many decades, physicians in general have recognized the importance of absorption as the cause for toxemic manifestations incident to infections. Methods for preventing such absorption are so well known and widely practiced that they require no special emphasis.

The substances absorbed originate from 2 sources: (1) Products of bacterial metabolism and the substance of bacterial bodies. The Vaughans' studies on bacterial substances led them to the conclusion that all bacterial proteins are highly toxic. (2) Cytoplasmic substances and products of proteolysis of tissues damaged or rendered necrotic by bacterial growth and invasion.

The decline in temperature, relief of pain and restlessness, disappearance of toxemic manifestations and general clinical improvement which follow adequate drainage of abscesses or local areas of cellulitis, are phenomena with which most physicians are familiar. They need not be advised that infections in closed areas, such as the pleural and peritoneal cavities and in infected wounds, require drainage in order to minimize absorption. Obstetricians often remove retained decidua, clots and débris from the uterine cavity when infection has followed childbirth. One chief reason why dèbridement of lacerated wounds lessens the danger of shock and promotes recovery is that products of infection are absorbed in lesser amounts. Wounds cleared of all débris contain less material upon which bacterial growth may thrive.

Whether evidences of shock result from local infections depends upon the extent, character and severity of the infection. If these are such that life is endangered, evidences of circulatory failure, formerly attributed to myocardial inefficiency, may be expected. The approach of death is heralded by the usual signs of shock, though the early manifestations of it often are masked by the fever and other disturbances resulting from the infection. Quite frequently shock develops gradually and in a sublethal degree and its presence is unrecognized although pulmonary congestion, edema and evidences of renal disturbance are known to be present. The frequency of terminal pneumonia (see Chapter XIV) in such cases is highly significant.

The occurrence of shock during severe systemic infections, such

as influenza typhoid, septicemia, yellow fever and others, was discussed in a previous chapter Unfortunately no measures for preventing absorption are available in systemic infections they are given such treatment as the internist may deem appropriate But extensive regional infections frequently produce exactly similar deficiency of circulation and other signs of shock. Examples of this are seen in puerperal infection lobar pneumonia, peritonitis and in wounds infected by such organisms as hemolytic strepto coccus, virulent staphylococcus gas-forming bacilli and others In certain of these, the prevention of absorption may produce marked benefit. Drainage and other appropriate measures may prevent death from peritonitis. Life may be saved if an extremity infected with organisms of fulminating virulence, is effectively drained or is amputated before the infection has spread to other parts of the body

It was observed in World War I that wounds infected with gas bacillus or with the bacillus of malignant edema often terminated in death by shock Early amputation or free excisions and drainage combined with injections of immune serums were some times effective in preventing the fatal outcome These experiences with anaerobic cellulitis and gas gangrene have been confirmed in World War II Quist wrote recently 'There is no doubt that if infective necrosis of muscle is present the only sure way of dealing with it is by adequate excision If it is localized to one muscle or muscle group, these may be removed if it is more extensive involving a segment or more of a limb, amputation is called for

The use of sulfa drugs locally in wounds constitutes a notable advance in combating infection as a major shock producing factor The growth of bacteria both saphrophytic and pathogenic causes rapid proteolysis of the substances of damaged tissues The ab sorption of such products from grossly contaminated wounds appears to cause more rapid and intense effects than those of simple autolysis of damaged tissue in the absence of bacterial growth This is illustrated in the milder effects of *crush injuries* (see pp 41 189) as compared with those of open contaminated wounds.

Débridement reduces this factor by the removal of devitalized tissue on which bacteria grow rapidly The treatment of open wounds with sulphathiazole or with sulphanilamide accomplishes the same effect and reduces greatly the tendency toward shock This is exemplified in the report on the treatment of casualties at

Pearl Harbor (Moorhead) and is advocated by the Committees on Chemotherapeutics and Other Agents and on Surgery, Division of Medical Sciences, National Research Council [300a]

Summary.—The prevention of absorption is of the highest importance in the prevention of shock

Débridement of wounds, whether incurred in battle or in accidents, lessens the absorption both of products of autolysis and those of bacterial growth Delay in the treatment of wounds results in higher mortality both from shock and from infections

The immediate local treatment of burns by coagulation tends to relieve pain, to prevent absorption, to lessen the local loss of fluid, to prevent infection and to facilitate healing with a minimum of scar formation

Intestinal obstruction by strangulation or by infarction requires prompt surgical intervention before the effects of absorption render the case hopeless Gangrene of the appendix or of a loop of bowel must be excluded by early operation if recovery is to be hoped for

The effects of simple obstruction may be reduced by decompression, this is followed by clinical improvement which allows time for accurate diagnosis and provides more favorable conditions for operation

The prevention of absorption from infected areas has long been practiced by physicians and surgeons This is accomplished by drainage of exudates from abscesses, various types of cellulitis, empyema, and from other forms of local or regional infections The toxemia of gas bacillus infection may be reduced by excisions or by amputation

In each of the conditions mentioned, danger of shock is incurred if absorption is allowed to continue In each of them, the treatment should be directed toward preventing absorption as well as toward combating the circulatory deficiency

CHAPTER XX

HEMOCONCENTRATION

THE phenomenon of hemoconcentration has been imperfectly understood. Its occurrence and significance are not discussed in treatises on surgery, symptomatology, diagnosis, nor on hematology. Hence it seems appropriate to review some of the observations found in medical literature. This phenomenon should not be confused with the *persistent* erythrocytosis seen in chronic CO_2 poisoning, cardiac deficiency, emphysema, in those who dwell in high altitudes and in polycythemia vera. Those interested in these conditions are referred to reviews by Weber and by Harrop.

HEMOCONCENTRATION IN SHOCK

Sherrington and Copeman (1893) found the specific gravity of the blood increased during the development of experimental shock. Cobbett (1897) confirmed that finding and noted that this occurred much earlier than the decline in blood pressure which is generally used as a criterion for shock. King (1902) noted erythrocytosis after surgical operations in a series of cases. The red cell count of one patient, who died in shock thirty six hours after operation, increased by 2,100,000 cells. The increase was less marked in non fatal cases.

Vale (1904) found that the specific gravity of the blood increased in both experimental and clinical cases of shock from various causes including surgery, trauma, burns and peritonitis. This returned to normal when the animal or patient recovered. He believed that the increase resulted from damage to capillary walls. He was the first author to suggest the clinical use of this test for the recognition of shock and for its differentiation from hemorrhage.

Crile (1909) found the number of erythrocytes increased during shock and decreased after hemorrhage. Henderson (1910) noted the same feature and attributed it to the escape of plasma from the blood into the tissues. Mann (1914) reported an increase in the specific gravity of the blood of animals in experimental shock. These findings were confirmed by the Special Committee for the Study of Shock and Allied Conditions during World War I (see Chapter VI). Hemoconcentration was found to be the earliest

sign of shock in wounded soldiers and was used practica
detecting the condition and differentiating it from hemoi
Erlanger and associates noted hemoconcentration regul:
experimental shock induced by trauma, by retarding the c
tion mechanically or by injections of adrenalin Maso
associates produced shock in dogs by the autolysis of live
stance *in vivo* and by injecting extracts of liver intraven
Increased concentration, decreased plasma volume and d
coagulation of the blood occurred regularly Coonse and
ciates corroborated the finding of hemoconcentration in (
mental shock Seeley, Essex and Mann produced shock i
in order to study the contributory effects of anesthesia
recorded hemoconcentration in each instance

Von Bergmann emphasized the fact that circulatory .
resulting from histamine, peptone, products of protein cle:
severe infectious diseases, physical trauma, burns, food poi:
as with B paratyphosus, influenza, sepsis and various tc
states, is different in character from the effects of hemor
In the former conditions there is endothelial damage result
leakage of plasma, decreased blood volume and hemoconcent
as shown by the hemoglobin content and erythrocytic coun
noted that hemorrhage was followed by hemodilution

Scudder became interested in hemoconcentration as seen
circulatory collapse produced by cholera Later he demons
hemoconcentration incident to intestinal obstruction, l
intoxications and in surgical or traumatic shock He found
this appears early, hours before the pressure declines, and t
differentiates shock from the effects of hemorrhage Fo
reason he urged that observations on the concentration (
blood should be used as a guide to therapy when circu
deficiency develops from any cause

Walther noted concentration of the blood and loss of p
as characteristics of true shock He observed that hemoconc
tion subsided when recovery from postoperative shock occ
Allen produced shock in rats by obstructing with a rubber
the circulation of a leg After five or six hours of obstructi(
removal of the tourniquet was followed by the developm(
shock. In these experiments Allen used hemoconcentratioi
criterion of shock The red cells progressively increased
8 million to 10, 11 or 12 million at death It was noted th:
blood was dark and thick and that clotting was delayed.

Eppinger gave detailed consideration to circulatory co

developing in a wide variety of clinical conditions They included trauma, burns, severe infections, poisoning with various drugs and from food, sunburn, toxic jaundice diabetic coma, urticaria and others The total volume of blood was decreased in all such cases. He found hemoconcentration in all cases of shock regardless of the condition causing it. This was attributed to increased permeability of the capillary membranes, with resulting leakage of plasma into the intercellular spaces

Blalock and associates found increased concentration of the blood during shock induced by trauma to muscles by burns of the skin and by intestinal manipulation They attributed it to local leakage of plasma into and about the areas of injury Harkins and Harmon reported experiments on animals and observations in human cases in which hemoconcentration was noted associated with shock like circulatory deficiency This occurred after burns, freezing, bile peritonitis tissue autolysis *in vivo* acute pancreatitis, pulmonary edema intestinal manipulation, mesenteric and portal obstruction, intestinal strangulation and after the release of an extremity from a constriction They investigated also the shock like circulatory failure which develops incident to acute peritonitis, experimentally produced They found the bleeding volume and the concentration of the blood were like those produced by other vascular poisons such as histamine. Andrews, Harkins Harmon and Hudson produced shock by subcutaneous injections of bile in dogs These developed symptoms of surgical shock, ending in death There was a marked increase in the volume of red cells shown by hematocrit readings in every case

The authors quoted in the preceding paragraph adhere to the interpretation that *local* transudation of plasma into the injured tissues causes the abnormal concentration of blood This interpretation disregards the evidence of capillary alterations in other areas. Colloidal dyes are useful indicators of capillary permeability When trypan blue or a similar dye is injected intravenously during the development of shock, the staining of the tissues is not limited to the injured areas but involves visceral regions remote from the injury Also direct examinations of the viscera during or after shock show capillary dilatation stasis, edema and petechiæ in the lungs, mucosæ, serosæ and in parenchymatous organs These findings indicate that the permeability of capillaries from which hemoconcentration results, is not limited to the region of the injury but occurs also in remote visceral areas.

Rose and Browne observed hemoconcentration as a prominent

clinical feature in shock from surgery, accidental trauma, intestinal obstruction, burns, mesenteric thrombosis and in acute peritonitis

The use of hemoconcentration as a practical criterion in experimental shock was exemplified in Chapters IX and X Its occurrence after burns was cited in Chapter XII Becky and Smitz, Simonart, Underhill, *et al*, Harkins, Ewig, Wilson, *et al*, Pack, Davis, Christophe and many others have confirmed the occurrence of progressive hemoconcentration following extensive burns

MISCELLANEOUS INSTANCES

The relationship of hemoconcentration to capillary pathology and to disturbed fluid balance was discussed in Part I, Chapters I and II *So long as the mechanism of fluid balance is functioning normally, concentration of the blood will not occur* It was shown that the various substances which affect endothelium deleteriously, alter the dynamics of fluid balance and of the circulation, these effects culminate in the syndrome of shock regardless of the nature of the agent or condition which damaged the endothelial membranes A few instances of such phenomena will be cited

Hemoconcentration has been noted by several observers in the group of conditions associated with hypersensitivity to various proteins Dean and Webb made observations on changes in the blood of 33 dogs during anaphylaxis They recorded a rise in the hemoglobin content and red cells after the injection of horse serum into sensitized dogs The hemoconcentration seemed to be proportional to the severity of the symptoms Simonds found an increased blood concentration and a reduced total blood volume during anaphylactic shock in dogs Similar findings were recorded after injections of peptone

Cantacuzene found that large doses of hemolytic serum (rabbit hemolysin) caused immediate death when given intravenously to rabbits Minute doses (0 03 to 0 1 cc) caused acute erythrocytosis ranging from 8,000,000 to 9,000,000

Eppinger noted hemoconcentration associated with urticaria in one case The red cell count rose from 4,400,000 to 5,700,000 at the height of an urticarial eruption Black and Kemp induced an acute allergic response by instilling pollen into the nostrils of a sensitive person This was accompanied by an increase in the specific gravity of the blood from 1 0561 to 1 0578 They found a similar increase in the density of the blood in 18 guinea pigs during anaphylaxis It was stated that the degree of this increase

was roughly parallel to the intensity of the reaction Meyler recorded hemoconcentration during anaphylactic shock in 2 patients after injections of horse serum

Krogh showed that capillaries may be injured directly by various substances, and Landis showed that any agent or condition injurious to capillary endothelium renders it abnormally permeable to plasma. Sollmann stated that irritant or corrosive poisons cause extensive vascular dilatation in visceral areas, and that death may occur from shock incident to this effect before the symptoms characteristic of that poison have time to develop Eppinger included poisoning with veronal, mercuric chloride and other poisons in his observations on shock. He noted that decreased blood volume, decreased volume flow, low blood pressure and hemoconcentration were present in such cases. He attributed these features to endothelial damage resulting in escape of plasma into the tissues. With these facts in mind it is pertinent to consider instances in which erythrocytosis has resulted from the effects of poisons.

It is known that acute poisoning with phosphorus often ends in circulatory collapse Early observers recorded red cell counts above 8 000,000 in such cases (Taussig, v Jaksch, Limbeck and others) Silbermann reported on polycythemia in phosphorus poisoning seen clinically in Prague He stated that the acute effects of phosphorus poisoning include the development of polycythemia. In 34 acute cases the red cell counts were above 6,000 000 and in 3 cases they were more than 8 000,000

Sollmann noted that poisoning with arsenic produces a pronounced and persistent fall in blood pressure He states that this is not due to cardiac failure nor to vasomotor deficiency but to paralysis of the capillaries with resulting loss of blood volume by transudation of plasma. It is recalled that Heubner also Krogh list arsenic among the "capillary poisons Rogers observed that arsenical poisoning produced circulatory collapse like that of cholera, accompanied by marked hemoconcentration Red cell counts above 8,000 000 were noted He recommended this as a diagnostic sign in arsenical poisoning The shock-like features which sometimes result from the intravenous arsenical medication are well known Moore recorded weakness, grayish cyanosis, cold clammy skin nausea, vomiting and syncope as the clinical features in such instances The blood pressure fell alarmingly and sometimes was unobtainable He noted further that the

clinical feature in shock from surgery, accidental trauma, intestinal obstruction, burns, mesenteric thrombosis and in acute peritonitis The use of hemoconcentration as a practical criterion in experimental shock was exemplified in Chapters IX and X Its occurrence after burns was cited in Chapter XII Becky and Smitz, Simonart, Underhill, *et al*, Harkins, Ewig, Wilson, *et al*, Pack, Davis, Christophe and many others have confirmed the occurrence of progressive hemoconcentration following extensive burns

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blood volume was reduced and that hemoglobin and erythrocytes were correspondingly increased, indicating concentration

Injections of bile intravenously, intraperitoneally or subcutaneously, will result in shock This is accompanied by marked concentration of the blood (Horall and Carlson, Harkins, *et al*) Sodium glycocholate will produce similar effects (Moon and Morgan) The venoms of various snakes cause endothelial injury and effect the circulation as does histamine Marked hemoconcentration is a feature in such experiments (Kellaway, Essex and Markowitz, Moon)

Lipsitz reported a case of accidental poisoning with tincture of cantharides Weak rapid pulse, subnormal temperature, thirst, vomiting and low blood pressure were prominent clinical features The red cell count reached 10,430,000 This subsided to normal as the condition progressed to recovery Cantharis, given by stomach tube to rabbits, produced "polycythemia" of several days duration In one instance the erythrocytic count rose from 5,560,000 to 9,800,000 Morgulis and Muirhead made further studies on the effects of cantharis on dogs and rabbits, and substantiated hemoconcentration as one of the features After fatal poisoning the visceral changes noted were identical in kind with those later described by us as characteristic of shock

Other poisons such as para-phenylene-diamine produce tissue edema and hemoconcentration by increasing endothelial permeability (Hanzlik and Tainter) Kilgore recorded occupational dye poisoning resulting in subnormal temperature and low blood pressure but no diarrhea nor vomiting In one such case with fatal outcome, the count of red cells rose from 4,416,000 to 9,100,000 Hamilton recorded moderate hemoconcentration in several types of occupational poisoning Davis noted an increase of about 20 per cent in the erythrocytes in experimental sublethal cobalt poisoning in dogs Eppinger gave allyl formate intravenously to animals This produced the characteristic syndrome of shock accompanied by hemoconcentration Edema of the tissues was demonstrated as in shock produced otherwise

Meyler published clinical observations on shock developing under various conditions of disease Cases of poisoning from veronal, mercuric chloride, arsenic and oxalic acid, presented the characteristic syndrome of shock accompanied by hemoconcentration A patient died in deep shock after an illness of twenty-four hours from paratyphoid B infection The red cell volume was 60 per cent and the plasma volume only 40 per cent by hematocrit,

the red cell count was 9,000 000 In another similar case the count was 8,000,000 Shock accompanied by hemoconcentration was described also in diabetic intoxication, in Addison's disease, in renal tuberculosis, in acute pancreatitis and in peritonitis.

The instances cited indicate that a varied group of chemicals and drugs possess the property of causing damage to endothelium This effect causes circulatory deficiency which frequently resembles shock and which is accompanied by hemoconcentration

Author's Experience —I have had opportunity to compare hemoconcentration with blood pressure readings in a number of

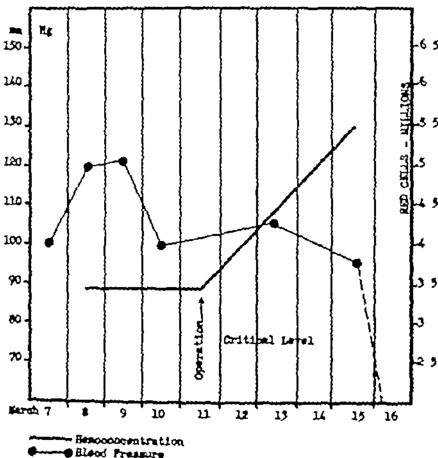


CHART 5 —Course of the blood pressure and hemoconcentration before and after operation (indicated by arrow) for relief of colonic obstruction due to carcinoma. Concentration of the blood began several days before the arterial pressure declined, and reached 40 per cent before the pressure sank below 95 mm. Hg

clinical cases during the development of circulatory deficiency of the shock type In each instance, examination of the blood forecast the development of the shock several hours to several days

before the blood pressure declined notably The course of the hemoconcentration and blood pressure, in one case, were described on p 126 A few other instances will be cited

A woman was admitted to the hospital (March 7) suffering from colonic obstruction Only two counts of red cells were made, one three days prior to, and another four days after the operation (Chart 5) In this instance the concentration of the blood gave

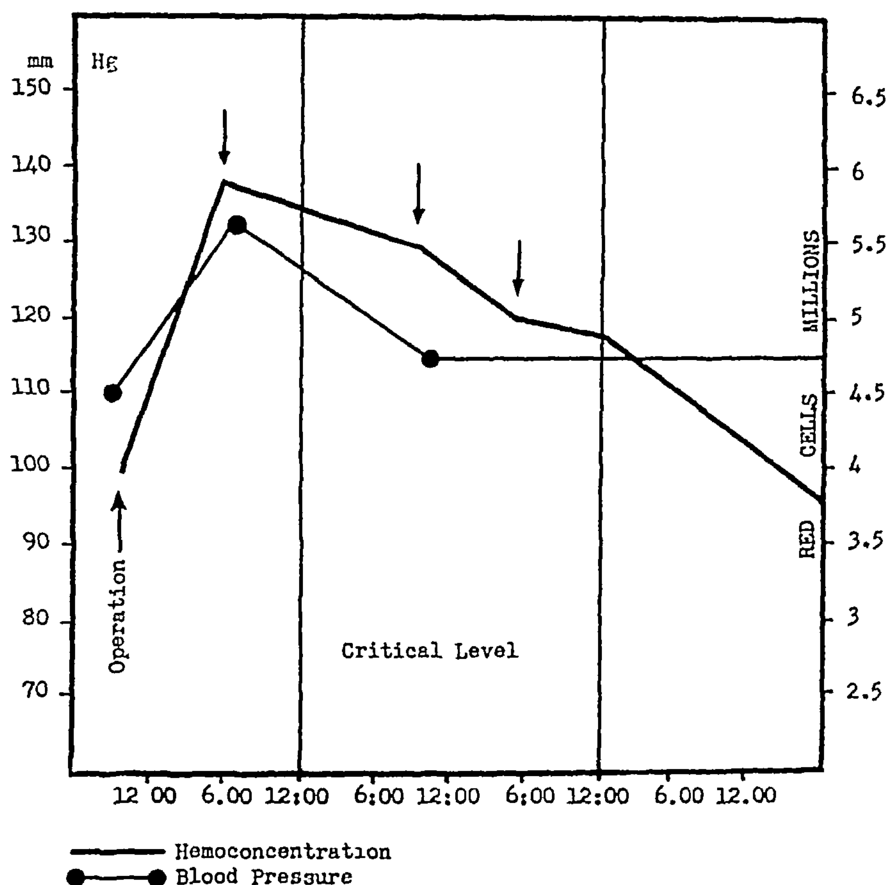


CHART 6 —The course of blood pressure and hemoconcentration after rectal resection (time shown by arrow) for carcinoma Hemoconcentration of 36 per cent developed in seven hours and indicated impending shock when the blood pressure was at its highest point Two transfusions and a saline infusion were given at times shown by arrows 1, 2 and 3, recovery followed

warning of circulatory deficiency four days before the blood pressure began its final decline In another case, rectal resection for carcinoma, hemoconcentration of 40 per cent occurred within a few hours, while the blood pressure was at its highest recorded point (Chart 6) Transfusions of blood and repeated intravenous

infusion of glucose-saline after the operation and on subsequent days, were followed by recovery

Circulatory failure incident to systemic intoxication was illustrated by an instance of icterus gravis with fatal termination on the fifth day of hospitalization The blood count on May 28 was 4 490,000 Two days later it had risen to 6 240 000—an

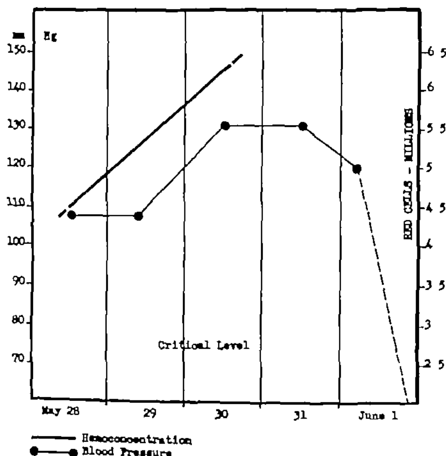


CHART 7 —The course of hemoconcentration and blood pressure during the development of shock from *icterus gravis* Only two counts of red cells had been made May 28 and 30 These showed that 40 per cent hemoconcentration was present when the blood pressure was at its maximum. This preceded by *two days* the fatal drop in arterial pressure.

increase of 40 per cent During this time the blood pressure *rose* from 110 to 130 mm of mercury Two days later the blood pressure had declined only to 120 but the decline continued precipitately ending in death (Chart 7) Hemoconcentration in this instance preceded the circulatory collapse by two days during which time the blood pressure gave no intimation of impending failure of compensation

I have performed or supervised numerous experiments in which data on the hemoglobin and red cell content of the blood were obtained with scrupulous care The features which bear upon the significance of hemoconcentration will be summarized briefly The experiments included finely ground normal tissues, such as muscle, liver, kidney and others introduced intraperitoneally, bile and its salts, peptone, bacterial cultures and toxins, histamine, moccasin and rattlesnake venoms injected intravenously or intraperitoneally, various poisons, emetin, veronal and other barbiturates given by mouth or by injection, burns, trauma to muscles, intestinal manipulation and strangulation, the effects of normal horse serum in sensitized animals, and the effects of deep roentgen irradiation given over the abdominal region

Such experiments were done on more than 350 dogs, 98 guinea pigs, 36 cats and on smaller numbers of rabbits, rats and monkeys Regularly and without exception, the agents and conditions mentioned produced hemoconcentration in each animal and species This appeared early and its degree was proportional to the apparent severity of the accompanying illness However, a considerable variation in the degree of concentration was noted in different animals of the same species For example, some dogs in the terminal stage of circulatory failure, resulting from the absorption of muscle substance implanted in the abdominal cavity, developed a concentration of only about 20 per cent In other dogs similarly treated, the concentration was over 40 per cent No reason for this individual variation was found

When recovery followed, the blood returned to its normal corpuscular composition When death resulted, the postmortem findings regularly showed evidence of capillary damage in visceral areas This evidence included serous effusions, dilatation of capillaries and venules with apparent stasis of blood in them, ecchymoses and edema in various tissues The edema fluid was shown to have a high protein content

The evidence summarized from published reports indicates that hemoconcentration is etiologically related to the mechanism by which circulatory failure of the shock type develops in a wide variety of clinical conditions Most authors attributed this directly to the leakage of fluid through endothelium which had been rendered abnormally permeable by injury

The experiments and clinical observations which I have recorded furnish direct support and confirmation for the interpretation

just given. Landis stated that the development of capillary stasis, seen in living tissues, is the surest sign of endothelial permeability It may be stated with equal assurance that hemoconcentration is the surest and earliest clinical sign of endothelial permeability in sufficient degree or extent to affect the efficiency of the systemic circulation

A rising curve of concentration is as ominous as a declining curve of arterial pressure But in many conditions *the former occurs early* and indicates the developmental stage of circulatory deficiency while the *latter indicates* the *failure* of *compensation* and the imminence of death

It is strange that a phenomenon which is so grave in its import, so common in its occurrence and so easily demonstrated has not been utilized by physicians in their clinical study of patients

TECHNIQUE FOR DETERMINING HEMOCONCENTRATION

Hemoconcentration may be demonstrated easily either by hematocrit determination of the volume of corpuscles, by the hemoglobin content by erythrocytic counts or by the specific gravity of the whole blood It is highly desirable to have a recorded reading, by whichever method is employed before the operation or the state of disease develops which may give rise to shock. Otherwise the degree of the concentration cannot be estimated accurately Such readings should be made routinely before each major surgical operation If either hemorrhage or shock or the effects of anoxia are feared, subsequent reading should be taken two hours after the operation and at intervals of two or three hours thereafter Observations on the concentration of the blood should be made as early as possible after burns or severe accidental injuries and at intervals of two or three hours subsequently

Examinations of the blood after operation may lead to erroneous conclusions if no previous examination is on record For example, a colonic resection was done for the relief of intestinal obstruction A blood count on the following day showed 4,600,000 erythrocytes which of itself would be regarded as a perfectly normal finding But when compared with a count of 3 400 000 before the operation it showed hemoconcentration of more than 35 per cent This indicated that the mechanism of shock was in operation but compensation was still effective as shown by a *rising* blood pressure Later the pressure declined progressively accompanied by the characteristic syndrome of shock with fatal termination

The technique for making hematocrit determinations, hemoglobin estimations and erythrocytic counts needs no discussion here Readings of specific gravity are quite simple when done by the method of Hammerschlag This consists in mixing chloroform with either xylol or benzine in such proportion that the specific gravity of the mixture ranges between 1 055 and 1 065 as shown by an ordinary urinometer Blood is drawn from a fresh puncture into a pipette and a drop of it is discharged below the surface of the mixture to avoid bubbles of air If the drop sinks, a small amount of chloroform is added to increase the specific gravity of the mixture, if the drop of blood floats, xylol is added When the mixture is adjusted so that the drop of blood remains suspended, neither rising nor sinking, it has the same approximate specific gravity as the fluid This is then determined by a specific gravity spindle Such determinations are sufficiently accurate for ordinary clinical purposes

An apparatus for determining specific gravity by the falling drop method has been perfected and may be obtained from dealers in scientific apparatus The use of this instrument in practiced hands results in more accurate readings than by the method of Hammerschlag

Variations in the specific gravity of the blood occur in a much narrower range than variations in counts of red cells For example, before operation or injury the specific gravity may be 1 054 and the red count 4,900,000 When shock has developed, examination of the blood may show 1 066 specific gravity and 8,000,000 red cells In this instance, the variation in the specific gravity was only 0 012 while that of the red cell count was 3,100,000 The index which provides the widest range minimizes the variations due to technique

A rise from 5,000,000 to 6,000,000 red cells represents a concentration of 20 per cent Such a finding indicates that the total blood-volume has been reduced about 10 per cent, and the plasma-volume about 20 per cent A hemoconcentration of 20 per cent is ominous, for it indicates that the mechanism of shock is in operation even though no decline in arterial pressure or other evidence of circulatory deficiency is shown Hemoconcentration of 40 per cent is a grave sign and is usually accompanied by other evidences of circulatory disturbance When the systolic pressure sinks below 70 mm Hg, the hemoconcentration may be anywhere between 40 and 60 per cent Concentration of 80 per cent has been recorded frequently in advanced stages of shock

CHAPTER XXI

EARLY RECOGNITION AND DIFFERENTIAL DIAGNOSIS

Begin the treatment of shock before its onset —FRAZIER

FRAZIER'S statement epitomizes his own experiences and those of other surgeons in dealing with this disorder In few conditions of disease is temporization or "watchful waiting more disastrous than in this If one awaits the full development of the clinical syndrome described on p 24 he will seldom treat a case of shock successfully The classical signs as set forth indicate that the mechanism of compensation has failed or is failing and that the 'cycle of death" is revolving inexorably The progressive ominous decline in arterial pressure and the accompanying evidences of circulatory deficiency are not signs of incipient shock they are signs of *departed opportunity*

Treatment to be effective, must precede the self perpetuating interplay of disfunctions which culminates in peripheral circulatory failure and which presently causes irreversible changes. The state of the circulation is not indicated accurately by the blood pressure for this may be well maintained or may actually *rise* during the incipient stage of shock. Wiggers noted a rise in the arterial pressure during the early stage of experimental shock Gray and Parsons noted evidences of shock when the blood pressure was at its *highest recorded point* and I have corroborated this observation in several clinical instances as related in the preceding chapter Cope observed that a decline in arterial pressure is not an accurate criterion for it is possible to have a fully developed state of shock with a blood pressure that is well maintained Blalock stated ' the blood pressure is an inadequate guide to the state of the circulation in incipient shock.

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capacity of the vascular bed increases until it is no longer compensable. Then the blood pressure sinks progressively and the clinical signs of shock become unmistakable.

It is highly important to recognize the *incipient* stage of shock and to begin its treatment before the mechanism of compensation becomes ineffective. It is essential to know the various conditions under which shock may be expected to develop, when treating a case presenting one of these conditions, the physician must be alert to recognize signs of incipient circulatory deficiency. Usually the state of the blood pressure is not a reliable criterion at the time when treatment may be most effective.

Freeman showed that a decreased volume flow of blood in the peripheral arteries preceded a decline in the arterial blood pressure when shock was developing. He recommended this as the earliest detectible clinical sign. However, the use of this criterion appears to present two disadvantages. No simple apparatus for determining arterial volume flow is available in physicians' offices nor in most hospitals, military or civil. Peripheral blood flow is reduced both in "primary shock," after hemorrhages and in true secondary shock, hence it would not serve to differentiate these conditions.

Our experiences as summarized in the preceding chapter, indicate that observations on hemoconcentration are most useful as indicating the incipient stage of shock. Physicians, internes and technicians are capable of making hemoglobin readings or counts of erythrocytes, many institutions have facilities for making determinations of specific gravity and of cell volume by hematocrit. The presence of hemoconcentration or hemodilution may be shown quickly and with sufficient accuracy by either of these methods. A discussion of the differentiation of shock from "primary shock" and from the effects of hemorrhages follows.

INITIAL OR PRIMARY SHOCK

For almost a century this has been recognized as a sequel to burns, visceral perforations and wounds, both trivial and serious. Immediately after injury, the victim often presents the clinical signs of shock including profound weakness, pallor, perspiration, a weak rapid pulse which may be imperceptible at the wrist, and a low arterial blood pressure. Psychologic or emotional reactions, as pain, fright, grief, the sight of blood or of a mangled wound, may cause the same reaction. The origin and nature of this response are essentially the same as of fainting or syncope.

This circulatory depression is usually transitory and not accompanied by disturbance of fluid balance nor other serious manifestations. When treating an injured person in this state, it was the practice of early surgeons to "wait for the reaction' because operations during primary shock often led to unfavorable results. The "reaction" was marked by the disappearance of the signs mentioned and by an apparent return of circulatory efficiency

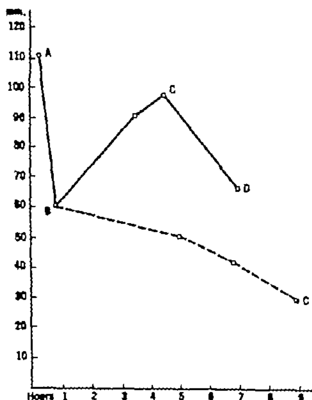


CHART 8.—This illustrates the development of initial shock, A—B immediately after the wound was received, A. The course B—C represents the recovery from initial shock followed by and the development of secondary shock, C—D The course B—C' represents the development of secondary shock without an interval of partial recovery

The occurrence of primary shock and its differentiation from true or secondary shock become matters of genuine importance when dealing with battle casualties and traumatic injuries in general Groeningen (1885) stressed the importance of distinguishing between this condition and delayed shock or 'wound torpor , he emphasized that the latter seldom develops within four hours after the wound was received and was a far more serious condition

These observations were substantiated by military surgeons during World War I It was noted that primary shock often appeared

promptly after severe wounds This was marked by a precipitate drop in the blood pressure accompanied by the other manifestations described above (see Chart 8) The fall of the blood pressure from A to B was usually followed by the rise from B to C, after which a more gradual decline from C to D accompanied the development of secondary or delayed shock In very severe injuries, as of the abdominal or cranial organs, no intervening rise occurred and the development of true shock was shown by the curve B–C[1] It is understandable that, if the circulation is depressed during a period of several hours, anoxia may develop in such a degree or extent as to affect endothelial membranes deleteriously and thereby to cause the serious type of peripheral circulatory failure [1]

Phemister and Livingstone endorse the division of shock into two classes: *Primary*—those cases that develop rapidly and are brought about by activity of the nervous system. *Secondary*—those cases caused by other blood pressure-lowering factors, as reduction of body fluids, anesthesia, toxins, extensive edema and certain endocrine disturbances "At any stage of the syndrome, secondary shock may be super-imposed on primary shock or *vice versa*" Psychic effects on the medullary centers, caused by pain or fear, injury or operation, may cause a fall in the blood pressure, bradycardia, pallor and faintness, which are prominent items in the syndrome of shock. Abdominal injuries or operations, especially those on the stomach and biliary tract, may cause these reactions, probably by stimulation of the autonomic fibers of the vagus nerve They state that these depressor effects are usually transient and of minor importance but, if other pressure-lowering factors are super-imposed, a marked state of secondary shock may develop

Cope's analysis of the subject is essentially in agreement with that given He stated that primary shock occurs frequently in abdominal emergencies such as acute pancreatitis, wounds, perforations, mesenteric thrombosis, or the sudden strangulation of a loop of bowel In such instances the sharp pain, incident to stimulation of the mesenteric and peritoneal nerves, may excite vasomotor reflexes which result in immediate or primary shock This usually is temporary, followed by a reaction with restoration of circulatory efficiency; but it may persist and merge over without interval into the grave condition of delayed or secondary shock.

[1] The data for Chart 8 were taken from Medical History of the Great War, Surg I, p. 73, H M Stationery Office London, 1922

Blalock has discussed this phenomenon under the heading *Neurogenic Shock* He stated that its onset is rapid and that it is much less serious than secondary shock since the blood volume is not essentially affected. "The primary alteration is vasodilatation dependent on diminished constrictor tone as a result of influences acting through the nervous system. In other words the decline of blood pressure is the primary circulatory disturbance Uncomplicated neurogenic alterations in the circulation in patients are usually of only short duration ' He mentioned trauma to the nervous system, spinal anesthesia, a severe blow to the abdomen surgical exploration of the peritoneal cavity psychic influences as in syncope or fainting and postural hypotension as instances of its occurrence.

These observations are in agreement with other discussions of this phenomenon However the designation *neurogenic shock* may cause confusion because trauma or surgical operations involving the brain cerebral hemorrhage and other types of neurologic lesions sometimes cause *true secondary shock* accompanied by hemoconcentration and by the visceral changes distinctive of that condition In other words some cases of secondary shock are *neurogenic* To avoid this confusion it might be well to use either the designation *initial shock* or *primary shock* for this type of circulatory disturbance

Circulatory disturbances resulting from severe burns conform to the principles discussed Initial or primary shock occurs at once or soon after the accident, after which the blood pressure usually follows one or the other of the courses represented in Chart 8 Wilson, McGregor and Stewart noted that changes in the concentration of the blood were slight or absent in initial shock while in secondary or delayed shock, the hemoglobin increased by from 15 to 150 per cent.

Recent observations (Grant, Florey) on air raid casualties in England indicate that some confusion has arisen and that surgeons in the emergency stations and hospitals had difficulty in evaluating the condition of victims brought in for treatment. Many of these were seen within an hour after the bombing they were in a clinical state of shock, yet there was no evidence of significant hemoconcentration Among those whose circulation seemed affected in similar degrees, as judged by blood pressure, pulse peripheral temperature and other clinical signs some responded readily to warmth fluids by mouth and transfusions of serum while others were irresponsive, continued in an unfavorable con

dition and often died Grant frankly admitted the difficulty encountered in estimating the seriousness of the shock although he saw and attended numerous cases

The published data do not indicate that examinations of the blood were made either routinely or frequently. It can be suggested that perhaps valuable experiences during World War I had been overlooked The cases seen within three hours probably represented initial or primary shock excepting those presenting severe abdominal or cranial injuries Hematocrit readings, hemoglobin estimations or erythrocytic counts, had they been made at frequent intervals, might have served to indicate the onset of delayed shock and to differentiate this from the primary shock in which no significant blood changes occur

Abnormal capillary permeability seems to be an essential factor in the mechanism by which true shock develops Primary shock and syncope appear to be transient vasomotor phenomena in which no qualitative changes occur in the capillary walls nor in the blood. These conditions are not serious as compared with that in which the minute vessels are both dilated and abnormally permeable The clinical differentiation of primary shock should not be difficult, and the presence or absence of hemoconcentration should be diagnostic

The full value of hemoconcentration as an index of the condition of the circulation can only be shown by making examination of the blood of the injured persons when first seen, and subsequently at intervals of one, two or three hours thereafter. Lacking such data isolated or sporadic examinations of the blood will neither evaluate the patient's condition nor the significance of hemoconcentration as a clinical sign Opportunities such as our British colleagues describe are advantageous for collecting such data.

DIFFERENTIATION BETWEEN SHOCK AND HEMORRHAGE

The similarities and distinctions between shock and the effects of hemorrhage were set forth in Chapter IX Clinically the two conditions resemble one another so closely that many have regarded them as identical It is highly important to determine which of these is responsible for the circulatory deficiency in a given case. Archibald stated "Hemorrhage has nothing to do with pure traumatic shock, although it may aggravate that condition It (hemorrhage) can be recovered sufficiently easily with blood

transfusions." The fact that the effects of hemorrhage are far less grave and far more responsive to treatment than those of shock, emphasizes the necessity for accurate differential diagnosis.

Loss of blood by hemorrhage results in dilution of the circulating blood because fluid is absorbed rapidly from the tissues to compensate the lost volume The degree of the hemodilution tends to be proportional to the amount of blood lost. Thus after hemorrhages amounting to 25 per cent of the total blood volume, the hemoglobin and erythrocytes will be found at about 75 per cent of their former levels.

This effect has been known for years yet very few physicians or authors realize the speed with which it is accomplished Adolph Gerbasi and Lepore made determinations of blood volume before and after hemorrhages in dogs of large size After hemorrhages amounting to 35 per cent of the blood volume, the dilution required about twenty two minutes for approximate completion

Robertson conducted a series of similar experiments on cats to determine how soon the blood volume is restored after hemorrhages. He found that the transfer of fluid from the tissues to the blood occurs *while the hemorrhage is going on* The blood drawn at the end of a single bleeding was more dilute than that at the start. He stated that the dilution occurs as rapidly as the blood is lost except when from 32 to 37 per cent of the blood volume had been withdrawn Hemorrhages up to 30 per cent of the total blood volume were accompanied by a *rise* in blood pressure In some instances, five minutes after severe hemorrhages, the blood volume actually exceeded the original blood volume He concluded

"The return of the blood or plasma volume to normal must depend on adequate fluid reserves in the tissue spaces

If these fluid reserves are sufficient it has been demonstrated by the above experiments that, after blood loss, the return of the blood volume to normal is practically immediate. The contrast between hemodilution after hemorrhages and the hemoconcentration during shock is shown diagrammatically in Figure 7, p 100

Simple examinations of the blood will usually differentiate between circulatory deficiency resulting from hemorrhage and that resulting from shock In the former the blood is *below* in the latter *above*, its normal or previous concentration. It may happen that the effects of hemorrhage are combined with the mechanism of shock. Such a combination is indicated by a *less marked* change in concentration Therefore when circulatory

deficiency is developing, and yet the blood is only moderately above or below the concentration shown prior to operation, there is evidence that shock is combined with the effects of hemorrhage.

Summary.—The successful management of shock requires that the condition be recognized in its incipiency This necessitates knowledge of the various circumstances under which it may occur and alertness to detect its onset A decline in arterial blood pressure is not dependable as a criterion of incipient shock

We have produced shock experimentally in animals by means of some 20 different agencies Thousands—literally—of tests for hemoconcentration have indicated its usefulness and dependability as a criterion under experimental conditions These, supported by clinical and experimental data, have established beyond question that shock and the effects of uncomplicated hemorrhages produce changes of opposite character in the concentration of the blood Hemodilution occurs *immediately* after hemorrhages

The responsibility for determining the value of this test in the clinical recognition of shock and in its differentiation from primary shock, must rest upon clinicians and surgeons They alone have opportunity for collecting sufficient data upon which to base dependable conclusions

Vomitus containing brown flecks—"coffee grounds"—which contain hemoglobin, is a valuable indicator of impending or incipient shock. In the absence of nephritis the presence of oliguria, concentrated urine containing pigment, albumin, débris and casts, and a progressive increase in the non-protein nitrogen content of the blood strongly suggest the presence of shock in a sublethal degree

CHAPTER XXII

THERAPEUTIC AGENTS IN THE TREATMENT OF SHOCK

Symptomatic.—Attempts to treat shock "symptomatically" resulted in the use of various drugs with the intent or hope of correcting one or another of the prominent clinical features. Physicians long have recognized the decline in blood pressure weak rapid pulse and other signs of failing circulation which indicate the approach of death in many forms of grave disease Formerly these signs were thought to indicate cardiac inefficiency Although that interpretation has been disproved many times, some still seek to secure "improved cardiac action" by the use of digitalis. Attempts to treat peripheral circulatory failure by such methods indicate a naïve confidence in the omnipotence of drugs Surgeons who have had long experience regard digitalis as useless and sometimes dangerous in the treatment of shock

The use of vasoconstrictor drugs such as epinephrin is equally illogical It should be remembered that the arteries, down to the finest arterioles are not dilated but are maximally contracted in shock. Incipient circulatory deficiency from any cause excites physiologic reactions for compensating it. These include activity of the sympatho-adrenal system which causes vasoconstriction, stimulation of cardiac action and the discharge of blood from the reservoir organs Moore found adrenin ineffective in the treatment of experimental shock He attributed this to the fact that, in shock maximal vasoconstriction had already occurred, this could not be increased by the effects of adrenin This conclusion has been corroborated by others. The use of vasoconstrictors under these conditions is not only useless it may be harmful Let it be recalled that one experimental method for *producing* shock is to give epinephrin in large doses or continuously Sollmann stated that the use of epinephrin in shock is essentially useless because it does not relieve the chief causative condition—the loss of capillary tonus He concluded that the danger exceeds the possible benefits.

Surgeons and clinicians rely greatly upon epinephrin in unfavorable responses to transfusions in serum sickness and in some types of urticaria Probably its use in these instances has been

justified by beneficial results When so used, a single physiologic dose should be given and this should not be repeated within an hour If benefit did not result from a single dose, further administration of epinephrin is useless and may be dangerous Careful reading of some reports on deaths from serum sickness arouses the misgiving that the excessive repeated injections of adrenalin may have been a factor in causing the fatal outcome Such large doses might well cause shock by excessive vasoconstriction in a healthy person

The principles just outlined do not apply to the use of such an agent as neosynephrin to combat the vasodilatation which occurs during spinal anesthesia The moderate decline of blood pressure incident to spinal anesthesia is not due to the same mechanism as shock, but it may contribute to the latter Anesthetists have found neosynephrin useful and free from ill effects when given for this purpose The use of morphine to allay pain and to relieve fright or apprehension is of unquestionable value But effects beyond these should be avoided rigorously because such effects reduce the activity of the respiratory center This results in decreased respirations and in a tendency toward anoxia The importance of avoiding the latter is obvious

Stimulants.—Stimulants such as strychnin or caffein have been used by some in attempts to counteract the profound depression which is a prominent clinical feature However, there is no evidence that these or other stimulants influence the tonus and permeability of the capillaries or that they increase the efficiency of the failing circulation The practice of giving warm sweetened tea or coffee to wounded men, immediately as they are brought to regimental aid posts or casualty clearing stations, was found beneficial in World War I, this had been confirmed in the treatment both of air raid casualties and of wounds and burns received in battle in the present war Usually the wounded will both take and retain such drinks (Brown, Dennison, Ross and Devine); the effect of these is not to combat the shock but to give comfort, warmth, fluid and nourishment which aid in preparing the wounded for operation

Mechanical Aids—Efforts have been made to facilitate mechanically the return flow of venous blood from the periphery Eppinger suggested elastic binders applied to the abdomen and sand bags applied to the limbs It is common practice to elevate the foot of the bed so that gravity will aid the venous return flow. The rationale upon which these procedures are based is not

entirely sound, it does not recognize that the sequestration of blood in the periphery occurs not in the venous channels but in the capillaries Stagnation or stasis of blood in the visceral capillaries is not readily affected either by gravity or by external pressure Also congestion of blood in the pulmonary circulation is a prominent feature in shock, this cannot be benefited readily by posture or by gravity

Elevating the feet or placing the patient in the Trendelenburg position favors recovery from syncope, initial or primary shock but it has not been shown to be an effective aid in peripheral circulatory failure Cannon reported that elevating the foot of the bed caused little improvement of the condition of soldiers in shock, though it is of value in syncope or pseudo-shock

Oxygen.—The importance of *oxygen lack* in any type of circulatory deficiency can scarcely be overemphasized Physiologists have recognized this for many years and have indicated several ways in which normal processes are affected by a deficient supply of oxygen One of these is the decreased alkaline reserve and tendency toward acidosis. Not only is metabolism lowered and the functional activity of all tissues depressed but the lack of oxygen results in incomplete oxidation and in the formation of abnormal catabolic products Deficiency of oxygen impairs the ability of the cells to maintain normal ionic concentrations within the cytoplasm This results in a disturbance of electrolytic balance between the cells and the extra-cellular fluids. Of paramount importance is the effect of anoxia upon capillary endothelium As discussed in previous chapters, this effect supplies the self-perpetuating feature which causes the circulatory deficiency to progress in the manner of a vicious circle

In view of these considerations it is not strange that those having to do with the practical management of shock recently have emphasized the value of oxygen in its prevention and treatment This principle was verified in a series of experiments (Schnedorf and Orr) in which oxygen was given by inhalation to dogs in shock. The blood pressure was maintained at a higher level and the dogs lived longer than those similarly treated but without oxygen Similarly, dogs given oxygen by inhalation tolerated more severe hemorrhages than did the controls These authors endorse the inhalation of oxygen in high concentration in the treatment of traumatic shock. Wood Mason and Blalock tested the effects of oxygen in the treatment of hemorrhage and of experimental shock. Their results confirm the experiences of others,

that the inhalation of oxygen in high concentration is distinctly beneficial in the treatment of these conditions.

Boothby, Mayo and Lovelace discussed both the physiologic and the practical aspects of oxygen therapy. They endorsed the rationale and substantiated its usefulness in surgical practice They stated that in traumatic cases, either military or civil, the administration of 100 per cent oxygen not only combats shock but aids in preserving the tissues of the injured extremity Charles W Mayo stated that it was then (1939) his custom to give oxygen by inhalation immediately to all patients who had undergone an extensive surgical procedure He found this routine practice of unquestioned benefit and regarded it not as an additional measure for treatment when shock has developed but rather as a measure for prevention

The administration of oxygen was facilitated by a mask with reservoir bag and tubes for connecting the apparatus with the standard oxygen tank The authors used inhalation of oxygen in conjunction with the Wangensteen or Miller-Abbott tube for the decompression of intestinal obstruction In some instances the inhalation of oxygen alone reduced the distention The conditions benefited or prevented by early inhalation of 100 per cent oxygen were traumatic or surgical shock, abdominal distention incident to obstruction, and severe acute infections

Scudder found inhalation of oxygen beneficial in the treatment of shock resulting from trauma, burns, intestinal obstruction and pancreatitis, also after hemorrhages The usefulness of oxygen in the treatment of injuries incident to warfare is indicated in a memorandum on the Treatment of Wound Shock issued (1940) by the British Medical Research Council They recommend that oxygen mixed with CO_2, 5 to 7 per cent, be given to those in whom the development of shock is feared as well as to cases in which the circulation already is deficient McMichael advocated the administration of oxygen by means of an inhalation mask for the prevention and treatment of shock among air raid casualties Shepherd reported obvious and immediate benefit among such casualties when given oxygen by means of the B L B mask This was used as a means for improving the condition of the wounded, preparatory for operative procedures This pr[illegible] as applied both to injuries and to burns, was endorsed [illegible] in prominent journals

Adrenal Cortical Hormone. - The rationale for the u[illegible] substance in the prevention of shock, is as sound phys[illegible]

as that for the use of oxygen Likewise the clinical results indicate marked beneficial effects.

The evidence indicating that one function of the adrenal cortical hormone is to control the permeability of endothelium and of tissue cells, was summarized briefly in Chapter XVI Animals lacking this hormone develop a circulatory disturbance having all the physiologic and biochemical features of shock When these animals are supplied with an adequate amount of the cortical hormone, that syndrome disappears and the circulation and other functions return to normal One fundamental condition in the dynamics of shock is abnormal permeability both of endothelium and of tissue cells Hence the use of any agent which will aid in preserving the normal semipermeable quality of these structures appears basically sound

Pollak noted that cell permeability and electrolytic imbalance result from the effects of histamine narcotics, direct injury to cells (burns) and oxygen deficiency A cardinal function of cortical hormone is its influence in maintaining the normal state of semi permeability Lack of this may initiate a vicious circle leading to a fatal derangement of metabolism and of circulation He regards the use of cortical extract as fundamentally logical and reports practical corroboration for this in clinical cases

Meakins holds that the administration of cortical extract strikes at the root of the matter by its action in correcting abnormal permeability of endothelium and of cells. Reed reported the effects of cortical extract in 50 patients undergoing extensive gynecologic and general surgical operations of various kinds It was his impression that these patients were definitely resistant to shock and that cortical extract combined with fluids given intra venously was distinctly beneficial in the treatment of postoperative shock.

Selye attributes shock, from various causes, to relative insuffici ency of the adrenals, he believes that adequacy of these and of other defensive reactions result in a restoration of the disturbed functions to normal He and his associates (263[a b]) compared the effects of cortical extract (cortin) with those of desoxycorti costerone acetate[1] in counteracting the effects of shock producing agents in animals They found cortin highly effective in such

[1] *Desoxycorticosterone* is one of the substances secreted by adrenal cortical cells. This substance has been prepared synthetically and is available as desoxycorticosterone acetate. For the sake of brevity this will be designated by the abbreviation *d.c.a.*

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experiments but that d c s a was ineffective even in large doses They believe that some substances other than d c s a is responsible for the efficacy of adrenal cortical hormone in maintaining circulatory efficiency On the other hand, Fine and his collaborators reported that d c s a. tended to prevent the decrease in plasma volume which results from intestinal obstruction in dogs

Besser, on the other hand, did not observe significant benefit from the use of d c.s a preliminary to operation in a large series of cases The drug was given in a dosage of 5 to 10 mg intramuscularly at periods of twelve, six and four hours before the operation The incidence of shock in this group was only slightly lower than in a control group in which no d c s a was used

Wolfram and Zwemer found that cortin increased the resistance of adrenalectomized guinea pigs to anaphylactic shock. Dragstedt, Mills and Mead tested the effects of adrenal cortical extract upon dogs with intact adrenal glands They found that the prior administration of cortical hormone did not prevent anaphylactic shock but it tended to diminish the severity of the reaction Swingle and associates tested the action of cortical extract as modifying the effects of trauma, intestinal manipulation and other shock-producing agents upon adrenalectomized dogs. They reported that circulatory failure did not develop if the adrenalectomized dogs were primed with large doses of cortical extract before shock-inducing procedures were begun They concluded "the evidence would indicate a fundamental rôle of the adrenal cortical hormone in the maintenance of the integrity of some part of the peripheral vascular apparatus "

Weil, Rose and Browne observed the effects of cortin plus d c s a as compared with d c s a alone in the treatment of experimental traumatic shock They reported significant differences between those treated with d c s a combined with cortin and the untreated controls The results in animals treated with d c s a alone were not significantly different from those receiving no treatment

Perla and his associates observed the effects of cortin, d c s a and of saline solution, separately and in combination, upon histamine shock in mice and rats The combination of saline and cortin was more beneficial than either alone Similar results followed d c s a in combination with saline solution, while d c s a alone had only slight protective effect

They reported on the results of saline solution and d c.s a in the preparation of patients for severe surgical procedures They

stated that these were strikingly benefited in each instance, there was no evidence of shock, the blood pressure was well maintained and was even slightly elevated in some cases, the postoperative exhaustion and toxemia were reduced, complications did not occur and the recovery was more rapid as compared with surgical experiences in similar cases without the preparatory treatment

Scudder published detailed particulars concerning the treatment of some 27 cases of shock from various causes including traumatic, postoperative, burns, pancreatitis, intestinal obstruction and the effects of hemorrhage. He used cortin plus saline solution (5 per cent) routinely in these cases. Several of them received oxygen by inhalation also The results as shown by the clinical data were highly satisfactory Scudder considers this mode of treatment distinctly superior to the methods previously used.

Shock Caused by Burns.—The systemic effects of extensive cutaneous burns do not differ in any important particular from those of severe traumatic injury Each may be followed immediately by initial or pseudo-shock, and subsequently by peripheral circulatory failure, *i e*, delayed or secondary shock in characteristic form

The local treatment for burns was discussed in a previous chapter (p 238) The systemic treatment is based upon the same rationale as that for shock from trauma or from other causes The importance of systemic treatment is emphasized in the observations of Pack and Davis that it is 'penny wise and pound foolish to consume invaluable time in applying perfect local dressings while the patient is sinking into irrecoverable shock' The management of burns has been presented in excellent fashion by McClure and by Harkins (175[16])

Morphine is given guardedly but in sufficient amount to relieve pain. The tendency of this and of other sedatives to impair oxygenation must be borne in mind

The inhalation of oxygen is based upon the same considerations as set forth above Harkins states that it is of great value in all serious cases. If oxygen is to be given it should not be delayed for its efficacy in *preventing* the development of shock will be far greater than in restoring circulatory efficiency when deficiency has become evident.

The effects of adrenal cortical hormone have been tested more often in the prevention of shock following burns than in other conditions Wilson had the benefit of extensive experience in the

treatment of burns prior to the advent of hormonal therapy He and his associates published (1936) the recovery of 3 cases of such severity that a fatal outcome by any other treatment seemed inevitable F A Hartman reported the recovery under cortin therapy, of a child burned over about 30 per cent of the skin surface Subsequently Wilson and Stewart reported on a series of 41 burned patients, in 10 of whom the injury was extensive The treatment included intravenous infusions with and without d c s a The results indicated that the drug had a remarkably prompt and effective action in correcting the abnormal chemical features of the blood Also there was beneficial action on the circulatory failure provided that the failure was not already profound They reported beneficial effects from d c s a in cases of intestinal obstruction also, but no effects were seen in circulatory failure resulting from infections

Several recent reports have indicated that extensive cutaneous burns are an important type of battle casualty In the reports of Atkins, also of Brown and his associates, the wounded who were evacuated from Dunkerque in June, 1940, included many who had been burned seriously Brown and associates treated 20 extensive second and third degree burns among 500 wounded evacuees They reported that d c s a was followed by more striking improvement than that seen after treatment with cortical extract The dosage was 10 mg every four hours

Rhoads, Wolff and Lee reported details of the clinical management of 26 extensive burns All received the usual local treatment and were placed under a thermoregulated "cradle", the blood volume was restored by plasma infusions as discussed in the next chapter Seven of the cases were given adrenal cortical extract (eschatin) within a few hours after the burn This was given in doses of 5 to 10 cc every six hours to adults and in relatively the same dosage to children They state that these cases required less plasma to counteract the hemoconcentration than was required by other cases, also the circulation returned to normal in a shorter time

They concluded that cortical extract is of value in correcting the fluid shift after severe burns, that it appears to act by reducing the permeability of capillaries but that it is of no value in restoring the circulation unless an adequate volume of plasma is introduced at the same time They recommended cortical extract in the treatment of extensive burns for the following purposes To reduce the amount of plasma required t[illegible] he circulation

to normal, to reduce the loss of plasma by leakage into the tissue spaces, and to shorten the period when stagnant anoxia is manifested

Summary.—A critical examination of reports on the treatment of shock indicates that few therapeutic agents, prescribed "symptomatically", have proved beneficial. This generalization applies to epinephrine, digitalis and to stimulants in general. The effects of these agents may even be detrimental.

Morphine or other narcotics should be given only in sufficient amount to secure quiet and freedom from pain. Beyond this point narcosis is contraindicated.

It is not surprising that the therapeutic means which have proved useful both in prevention and in treatment are agents which counteract one or another of the major items in the dynamics by which shock progresses. Most important among these agents are oxygen, adrenal cortical extract and the restoration of lost blood volume.

Lack of oxygen is a highly important item in the mechanism of shock. The inhalation of oxygen aids materially in maintaining adequate circulation and in preventing serious cellular and metabolic abnormalities. It likewise tends to interrupt the operation of the vicious circle even after shock has been initiated.

One function of adrenal cortical hormone is to maintain the normal impermeability of endothelium and of cells. There is significant evidence, both experimental and clinical, that adrenal cortical hormone is highly beneficial in the prevention and in the treatment of shock. Whether the synthetic product, desoxycorticosterone, will prove to be as effective as cortical extract containing other active substances, remains to be determined.

One item of highest importance in the mechanism of shock, is the decreased volume of circulating blood. The restoration of this by giving plasma, serum and other fluids intravenously is discussed in the following chapter.

CHAPTER XXIII

TRANSFUSIONS AND BLOOD SUBSTITUTES IN THE TREATMENT OF SHOCK

THE RATIONALE OF FLUID REPLACEMENT

DIVERGENT views concerning the pathogenesis of shock are expressed by many writers, but all agree that a marked decrease in the total blood volume is one of its outstanding features This decrease is due in part to loss of blood or plasma at the site of operation or of trauma, to local loss of plasma in burned areas, and in part to extensive leakage of plasma in systemic areas as a result of increased capillary permeability The depletion of blood volume may be augmented by vomiting, diarrhea or by perspiration There is agreement also concerning the principles upon which therapeutic measures are based Regardless of the route by which the loss occurred, the immediate problem is to counteract it by the most effective means available Fluid must be supplied to replace that which was lost

The disturbance of fluid balance which accompanies shock, markedly retards the absorption of fluid given by the oral, rectal or subcutaneous routes Hence the administration of fluid by those routes is uncertain or ineffective This fact makes it imperative that the fluid be introduced directly into the blood stream, either intravenously or by injection *via* the bone marrow

In general, the more closely the fluid supplied resembles that which was lost, the more effective will be the replacement Thus after severe hemorrhages, a transfusion of whole blood is a logical means for replacing the loss It should be given in adequate amount and as early as possible after the hemorrhage occurs In, cases of shock without significant hemorrhage, plasma or serum is the ideal substance for replacement therapy

The tendency of shock *to progress* was noted in early times, was emphasized by investigators during World War I and has been verified by subsequent experiences The cause for this tendency was shown in Part I, its mechanism consists in the interplay of factors shown in the Vicious Circle (p 208) Treatment to be effective, must be administered early before a progressive decline in the blood pressure indicates failure of compensation Low arterial pressure is not a sign of incipient shock but of decompensa-

tion The period during which compensation is adequate does not last indefinitely the time will be short until progressive endothelial relaxation leads to stasis, anoxia and to irreversible changes After injury, the first six are the 'golden hours during which measures for prevention and treatment are most beneficial The effectiveness of these measures will vary inversely with the duration and the degree of shock.

The rationale of treatment may be summarized as follows (a) A prompt differentiation between *primary shock hemorrhage* and *secondary* or *delayed shock* Primary shock requires only restorative and supportive measures (b) Immediate treatment for preventing the progression of shock and for replacing the fluid lost whether by hemorrhage or otherwise (c) The continued use of appropriate fluids in sufficient quantity to maintain adequate blood pressure and circulatory efficiency

TRANSFUSION OF WHOLE BLOOD

The purposes and technique for giving whole blood by transfusion are too well known to require discussion here One condition in which this measure has been used effectively is that resulting from extensive hemorrhages Frequently this is associated with varying degrees of traumatic injury, hence the mechanism of shock is often combined with or aggravated by the loss of varying amounts of blood This combination is usually present in shock from wounds, accidental injuries or following extensive surgical procedures It then becomes a clinical problem to determine the relative importance of hemorrhage as a factor in the patient s condition An examination of the blood by hemoglobin estimation red cell count, specific gravity determination or by hematocrit will give an approximate evaluation sufficiently accurate for clinical purposes. It is highly important that this be done immediately because the mode of treatment and the amounts of blood or fluid required are determined largely by the results of such examinations. Also the subsequent requirements of the case are estimated by the same method Recent reports (Rhoads *et al* Harkins Elkinton *et al* Black and others) on clinical experiences with shock from trauma, burns and from other causes give formulæ for determining the dosage of fluids required in such conditions these formulæ are based upon hematologic examinations. It is important to examine the blood early and at intervals thereafter 'as a guide to therapy

It is well known that the condition of an otherwise healthy person does not become critical from hemorrhages until the red cells have been reduced to about one-third of the normal This statement applies to slow or successive hemorrhages, not to the sudden loss of a large volume of blood Certainly blood with a hemoglobin reading of 40 per cent can carry sufficient oxygen to maintain physiologic processes Hence if the red cells and hemoglobin have been reduced below 50 per cent, transfusions of whole blood represent the method of choice for raising the blood volume and maintaining adequate circulation

When the loss of erythrocytes by hemorrhage has not been excessive, plasma protein deficiency is the factor of major importance The physiologic mechanism for compensating loss of blood is a rapid shift of fluid from the cells and tissue spaces into the vascular system This fluid contains electrolytes in the same concentration as the blood, but its protein content is low, hypoproteinemia is the result Hence plasma protein supplied artificially restores the fluid of the blood to its normal composition and hastens recovery

Numerous experimental and clinical observations indicate that, unless there has been excessive loss of erythrocytes, the introduction of plasma or serum counteracts the effects of hemorrhages as effectively as transfusion of whole blood Levinson, Neuwelt and Necheles made an experimental study of this by comparing the effects of saline infusions, of serum infusions and of blood by transfusion after extensive hemorrhages in dogs The results showed that saline infusions were inferior but that serum infusions were equally effective as transfusions except when the erythrocytes had been reduced below the approximate limits mentioned This observation was confirmed by the use of serum after hemorrhages in clinical cases Buttle, Kekwick and Sweitzer made similar experiments on cats which had been bled 50 per cent of their total blood volume It was found that plasma was as efficacious as whole blood in restoring the animals to normal conditions They state that after hemorrhage of this degree, the replacement of red cells plays no vital part in the treatment Elliott, Tatum and Busby corroborated these findings and they have been confirmed by Amberson, Lee, Mudd, Flosdorf, Hill and others A bulletin issued by the Subcommittee on Shock, National Research Council, states "that blood plasma is approximately as effective as whole blood in the treatment of hemorrhage "

The agreement appears to be general that the intravenous

administration of saline solution aids in the recovery from slight or moderate hemorrhages, that infusions of plasma or serum are highly effective in restoring the blood volume and plasma proteins after severe hemorrhages and that transfusions of whole blood are needed only when the hemoglobin content and erythrocytes are below 40 or 50 per cent of the normal

The institution of blood banks in medical centers and hospitals has facilitated greatly the use of transfusions for all purposes Donor's blood is drawn aseptically into closed flasks containing enough sodium citrate solution to prevent clotting The blood is then typed tested for sterility and for Wassermann and Kahn reactions and is stored in refrigeration until needed Frequently several small hospitals collaborate to maintain a blood bank in one of them, thus serving the needs for transfusion in a city or large area of population A major advantage provided by blood banks is the saving of time in finding a compatible donor Another is the relatively simpler procedure of giving blood from a flask as compared with transfusion by the direct method from donor to recipient. The latter method requires an experienced operator the former is not beyond the capacity of an interne Concerning the usefulness and safety of citrated blood, it is stated by men of wide experience that transfusions by the direct method have no advantages whatsoever over those in which citrated blood is used

One disadvantage of the blood bank is the fact that erythrocytes develop abnormal fragility and presently undergo hemolysis when stored in refrigeration for a relatively short time This makes the blood unsatisfactory for use if not unsafe While some authorities use blood which has been stored for several weeks others regard it as unsuitable after five days (Strumia) or seven days (White) Formerly this situation caused large amounts of stored blood to be discarded now in many institutions the supernatant plasma is drawn off from the out-dated blood and is preserved and used as described in a subsequent section Failure to make use of this life-saving material is a culpable waste

Transfusions in the Treatment of Shock.—Efforts to treat shock by various means during the previous world war provided a foundation of experience upon which subsequent developments have been based Saline and colloidal solutions as well as transfusions were tried extensively It was found (Drummond and Taylor Keith) that transfusion of blood produced marked benefit in cases of uncomplicated hemorrhage that it produced fairly satisfactory results in hemorrhage combined with a moderate

degree of shock, but that cases of fully developed shock were not benefited by transfusions nor by any other mode of treatment

These observations have been confirmed by McDowall, also by Taylor (389*a*) in the treatment of experimental shock by transfusion This principle is widely accepted by those who are familiar with the mechanism of shock Some investigators (Freeman, Blalock) even used an unfavorable response to transfusion as a *criterion of shock*, if animals with impaired circulation and low blood pressure recovered when transfused, shock was regarded as absent, if the circulatory deficiency progressed fatally in spite of transfusions, the animal was in shock There may be objections to this as a criterion, but the instance illustrates the ineffectiveness of transfusions in counteracting a serious degree of secondary shock

When shock is not complicated by serious hemorrhage, transfusion of whole blood is not a logical measure There is no lack of red cells, on the contrary often there is marked hemoconcentration The addition of more erythrocytes will not relieve the viscosity of the blood but will increase the tendency toward stasis A transfusion may be detrimental rather than beneficial The increased volume of concentrated blood throws an added strain upon the myocardium which may already be weakened by insufficient oxygen Fluid is urgently needed to restore the blood volume, to reduce the concentration and viscosity of the blood, to prevent or relieve stasis, and to interrupt the operation of the vicious circle The use of fluids is discussed in subsequent sections

SUBSTITUTES FOR BLOOD, PLASMA AND SERUM

Physiologic studies have indicated that the *physical* rather than the *biologic* properties of fluids determine their usefulness in the treatment of hemorrhage or shock This view has led to extended search for some organic substance suitable for use as a replacement fluid Taylor and Water have outlined the specifications required of a fluid for the purposes mentioned (*a*) Its molecular size when dissolved, must be such that it will not escape freely from the vessels (*b*) Its viscosity and osmotic pressure must approach closely those of the blood (*c*) It should be almost isotonic with the contents of the erythrocytes (*d*) It must be nonantigenic and perfectly innocuous The substance should be readily available and be capable of quick and easy preparation for intravenous administration To these requirements, we would

add that the substance should be capable of sterilization transportation and storage without deterioration, and that trial under experimental and clinical conditions should show benefit comparable to that resulting from transfusions with homologous plasma or serum

Saline and Glucose Solutions —During the previous war, physiologic and hypertonic solutions of sodium chloride alone and combined with glucose were given intravenously to counteract shock in wounded soldiers but with uniformly disappointing results A temporary increase in blood pressure and in the circulation resulted followed regularly by progressive deficiency of the circulation These results have been verified without exception in the experimental treatment of shock in animals Noncolloidal fluid leaks out through permeable capillary walls 'almost as fast as injected (Mann) Such treatment is not only useless it is positively harmful As the saline solution passes into the tissues it takes much of the plasma protein with it This depletes the plasma aggravates the hypoproteinemia and augments the edema.

In many surgical clinics, it is standard practice to give an infusion of glucose saline solution either before during or immediately after extensive surgical operations which may result in shock It is not possible to evaluate the actual benefits of this procedure clinically because test and-control conditions cannot be provided If the tissues are dehydrated or the blood sugar depleted the logic of the procedure would be unquestionable But if the operator believes he is able to modify osmotic forces preserve fluid equilibrium or maintain normal endothelial function by introducing either isotonic or hypertonic solutions of salt and glucose he should be disillusioned Physiologists have presented definite evidence that diffusible substances such as glucose and sodium chloride pass readily through the endothelium promptly equalizing the concentration of them in the blood and in the tissues. Also that the excess of NaCl and of water in the system, is excreted rapidly *via* the kidneys and that the excess glucose is stored as glycogen in the liver and elsewhere However the procedure is not open to censure on the ground that it is detrimental

Acacia.—The Committee on Wound Shock and Hemorrhage worked intensively on methods for treating these conditions during the previous World War Bayliss a member of this Committee investigated the physical and chemical properties of several colloidal substances which might be more effective than saline solutions He found that a sterile solution of gum acacia

in physiologic saline was well tolerated when given intravenously and that the effects were often beneficial Subsequently this method was used extensively in the treatment of wounded men The results were superior to those of glucose and saline solutions in replacing blood loss from hemorrhage but little or no benefit was seen in cases of severe shock Since that time acacia solution has been used with varying results Severe toxic reactions were reported by some while others observed no untoward effects Impurities in the product used and inaccurately buffered solutions were assigned as probable causes for the reactions A serious objection to the use of acacia is the fact that it is not readily eliminated from the system Extensive deposits of it occur in the liver and elsewhere If large amounts have been introduced, these may affect detrimentally the function of the liver and of other tissues

Pectin —Recently Hartman, Schelling, Harkins and Brush investigated the properties of pectin solution as a replacement fluid in the treatment of hemorrhage and of shock Pectin is a colloidal carbohydrate of high molecular weight and complex composition, obtained from citrus fruits They state that in solution 1 to 200 (0 5 per cent), it has about the same viscosity and osmotic pressure as whole blood Its physical properties are unchanged after sterilization by steam under pressure They found that pectin is non-toxic, non-antigenic, that it causes no untoward effects when given intravenously and that it is not retained in the tissues but is excreted readily, most of the amount injected was excreted in the urine within seventy-two hours A prompt and sustained improvement of the circulation followed the injection of 1 per cent pectin solution after hemorrhages, an increase in blood pressure and decrease in hemoconcentration followed its use in shock due to bile peritonitis in animals Favorable results followed its use in several patients in whom shock was imminent.

Hartman and Harkins have just reported details concerning the use of pectin after surgical operations, accidental injuries and in miscellaneous conditions in which shock was feared Their data are derived from more than 125 clinical cases There were no abnormal nor untoward reactions and the blood pressure was maintained at satisfactory levels The increased blood volume resulting from the infusion, did not subside rapidly as compared with cases in which glucose-saline solution was given They state that pectin solution has been substituted for glucose-

saline solution as a routine preventive measure after extensive operations in their surgical service

Gelatin —Gelatin has several of the properties required of a fluid to be suitable for transfusions Hogan (1915) described accurately the advantages of colloidal over saline solutions for intravenous use. He gave detailed instructions for the preparation and sterilization of purified gelatin in a 4 per cent solution This was used with good results and with no unfavorable manifestations in 9 cases of shock from various causes Bayliss (1917) found that a 6 per cent solution of gelatin has approximately the same viscosity and colloidal osmotic pressure as those of blood plasma Also it has very low antigenic properties animals treated with it do not become sensitive to subsequent injections However it is difficult to sterilize gelatin by heat without reducing markedly its viscosity and its osmotic pressure Also unless heated it has the property of jelling which renders the solution unsuitable for injection If these disadvantages could be obviated a properly purified gelatin might be a satisfactory replacement fluid for use in shock and after hemorrhages

Isinglass.—This substance is a form of gelatin obtained from the swim bladder of several kinds of fish It is available as an article of commerce Taylor and Water investigated the properties of purified isinglass and found that the colloidal osmotic pressure of a 7 per cent solution was closely similar to that of human plasma. Also it fulfilled the other specifications required of a fluid for transfusion purposes In tests on animals, it was found that a 7 per cent solution given intravenously restored the blood pressure and circulatory efficiency after hemorrhages which were fatal in the untreated animals

More recently Taylor reported on clinical results from the use of isinglass in more than 40 patients. The amount usually given at one injection was 500 cc of a 4 per cent solution A sustained increase in both arterial pressure and in blood volume regularly followed In one instance 1500 cc were given with excellent effect to a patient in traumatic shock No unfavorable reactions occurred in any case These results are the most significant that have been reported on the use of a gelatin for the purposes mentioned Further developments will be awaited with interest.

Hemoglobin Ringer Solution.—Sellard and Minot investigated the use of hemoglobin dissolved in Ringer s solution as an agent for the relief of anemia It was found that the oxygen-carrying capacity of this compared favorably with that of erythrocytes

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and that intravenous infusions of it were well tolerated by the animal organism Amberson showed that hemoglobin dissolved in sterile buffered saline solution presents several advantages as a blood substitute. The molecules of hemoglobin are of similar size to those of albumin, and its osmotic pressure is high Such a solution was effective after hemorrhages produced experimentally, animals survived after 85 per cent of their blood had been replaced by it, no unfavorable effects were seen Buttle and associates reported prompt recovery of the blood pressure in cats after hemorrhages amounting to 50 per cent of their blood volume, when treated with hemoglobin in solution, but the recovery was not well maintained in all cases and there were some respiratory disturbances They ranked hemoglobin-Ringer solution as superior to acacia and to saline solutions but inferior to plasma and to serum in replacing loss of blood by hemorrhage The use of hemoglobin-Ringer solution is still in the experimental stage

Bovine Plasma and Albumin.—The plasma and serum of several animal species have been given intravenously to man, often without untoward effects Horse serum is sometimes given to increase the coagulability of patient's blood, immune sera from horses, cows, goats and rabbits have been given intravenously to combat infections Three possible dangers attend such medication (1) The animal serum may contain hemolysins or hemagglutinins which affect human corpuscles (2) If the individual is hypersensitive to protein of that species, a severe reaction usually results (3) All such sera are antigenic, if at a later time a second injection of the same species serum is given, an anaphylactic reaction may be expected These principles should be held in mind when considering the intravenous administration of heterologous plasma or serum

Wangensteen and his associates (1940) investigated the possibilities of bovine plasma as a substitute for human plasma in restoring the blood volume after hemorrhages or in shock They reported that bovine plasma given intravenously to man in fairly large quantities, 750 to 1000 cc , is retained and apparently utilized without ill effects Subsequently (see Kremen, 1942) they reported on the administration of bovine plasma and sera, prepared and preserved in different ways, to a series of 120 human cases Varying types and degrees of reactions occurred in a majority of instances, some of these were described as serious but none were fatal The use of serum from which the hemolysins and hemagglutinins had been removed by adsorption with human erythrocytes,

reduced the occurrence of reactions from 66 4 to 24 5 per cent They concluded that the incidence of reactions was sufficient to contraindicate any clinical use of whole bovine serum or plasma at the present time They suggested that a preparation of bovine albumin (*vide infra*) separated from globulin may prove a safe and practical blood substitute

Cohn made intensive studies on the physical and biochemical properties of human, bovine and other plasma He states that the albumins represent over 60 per cent of the proteins in normal human plasma, but they give rise to a much greater proportion of the blood osmotic pressure by virtue of their smaller size and larger net charge. The albumins are by far the most important osmotic factor of plasma. Cohn has been able to prepare large amounts of relatively pure albumin by improved methods of fractionation He has shown that albumin so prepared is pure, as indicated both by its electrophoretic pattern and by sedimentation in the ultra centrifuge. A significant practical feature of this development is the fact, noted by Cohn that it makes possible various clinical investigations on the therapeutic uses of relatively pure albumin

Purified beef albumin is a promising substance for use as an agent in intravenous medication because of its physical properties of low viscosity, great stability solubility and osmotic activity For this reason Janeway and Beeson began investigations as suggested by Cohn They found that beef albumin maintained the blood volume and circulation of dogs in shock resulting from burns. They tested its effects in varying doses upon a group of 16 human subjects. No untoward reactions occurred except in one subject who they noted, had previously developed serum sickness from horse serum

Davis and associates (100[4]) prepared albumin from bovine serum by the usual methods of precipitation and filtration After tests for sterility this was given in amounts from 50 to 300 cc intravenously to 13 human subjects. No unfavorable reactions of any kind followed These results confirmed their conclusion from previous experiments that the globulins of bovine serum are responsible for its occasional toxic effects

The evidence cited indicates the possibility that bovine albumin if sufficiently purified may not produce the unfavorable effects which often follow the intravenous use of the whole plasma or of the imperfectly fractionated albumins Further evidence will be required before the safety and the clinical usefulness of bovine albumin can be evaluated

A substitute fluid which could be used safely and with good effect for transfusion purposes offers the obvious advantages of low cost and ready availability Physicians have frequent occasion to use intravenous therapy of this kind, were the means at hand The substances which at this time appear promising as blood substitutes are pectin, isinglass and purified albumin As yet, neither of them has been given adequate trial to establish its merits and its possible disadvantages in clinical use. The fact that gelatin and albumin may be utilized by the body as nutrition or as material for building more complex proteins, is a point of advantage over pectin and gum acacia None of these except the latter has as yet been prepared pharmaceutically for medical use Purified acacia, in ampoules with the appropriate amounts of sodium chloride and distilled water, has been prepared by reputable pharmaceutical concerns It should be at hand in hospitals and clinics for use in emergencies when neither human blood nor its derivatives can be obtained

HUMAN PLASMA AND SERUM

The blood volume of patients in true shock is reduced markedly by loss of plasma, hence the rational measures for counteracting this feature are obvious Authorities agree that in this condition the introduction of plasma is more effective than transfusion of blood except when the hemoglobin content of the blood has been reduced markedly by hemorrhage The desirability of replacing the lost volume by the introduction of plasma or serum has long been recognized, but means for accomplishing it have been developed only recently

Human plasma is obtained by drawing donor's blood into a closed sterile receptacle containing sufficient so[illegible] te solution to prevent clotting After the corpusc[illegible] the bottom, either by gravity or by centrifu[illegible] plasma is drawn off and pooled with th[illegible] a large container After bacteriologic[illegible] plasma is placed in smaller containers and [illegible] trated at room temp[illegible] in refrigerat[illegible] for dehydration a[illegible] e plasma trated to a frac[illegible] volume [illegible] completely bef[illegible] ny instit[illegible] banks are main[illegible] on purp[illegible] is used as a so[illegible] the bl[illegible]

for transfusions, the plasma is drawn off from these flasks and is then treated as described

Human serum is obtained by drawing donor s blood into a closed container allowing it to clot then withdrawing the serum This may then be treated as described for plasma and stored until needed The chief difference in the composition of serum and plasma is that the former contains no fibrinogen nor prothrombin while the latter contains a minute amount of sodium citrate It has been shown that neither of these differences affects their usefulness as therapeutic agents.

It has been found that no typing nor cross-matching of plasma with the patient's corpuscles is required Plasma pooled from a number of donors may be given intravenously to any recipient without regard to his blood type or group Reactions from incompatibility do not result

For a time there was much discussion as to the relative merits of serum and plasma. Those who were using either of these products were apprehensive concerning the occasional unfavorable results reported from the use of the other A disturbingly high rate of reactions was recorded by several writers (see Brown and Mollison, also Weil and Browne) after the use of serum Subsequently it was found (Mudd and Flosdorf Scudder and Self) that serum may provoke a reaction when fresh but that the same serum, stored for two weeks, was perfectly innocuous The quality which caused these reactions disappeared after a brief lapse of time Since ten to fourteen days are required for bacterial cultures to incubate, no time is lost by allowing the serum to age for two weeks before processing it.

It must be remembered that the entire technique for preparing and using these products has developed most recently and very rapidly It is natural that various unforeseen difficulties should occur The problems of detecting and removing the causes for these required time and experience As in many other fields, the methods first used were imperfect It is remarkable that most of the imperfections in the preparation of plasma and serum have been corrected in so short a developmental period

Undoubtedly many unfavorable reactions were due to bacterial contamination Over 8 per cent of some 6 000 liters of liquid plasma which was shipped to England in the early part of World War II was found contaminated in spite of the fact that merthiolate 1 to 10,000 had been added during the preparation of the plasma Novak has recommended the addition of sulfathiazole

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Human plasma is obtained by drawing donor's blood into a closed sterile receptacle containing sufficient sodium citrate solution to prevent clotting After the corpuscles have settled to the bottom, either by gravity or by centrifugation, the supernatant plasma is drawn off and pooled with that from other donors in a large container After bacteriologic and serologic tests, the plasma is placed in smaller containers and either stored unconcentrated at room temperature or in refrigeration or frozen If means for dehydration are available, the plasma may either be concentrated to a fraction of its original volume or it may be desiccated completely before storage In many institutions in which blood banks are maintained for transfusion purposes, the stored blood is used as a source of plasma When the blood becomes unsuitable

for transfusions, the plasma is drawn off from these flasks and is then treated as described

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to plasma and serum to prevent contamination However, it was shown (Heath and Province) that none of the sulfonamide derivatives in concentrations up to 0 2 per cent, exert sufficient bacteriostatic effect to safeguard stored liquid plasma against contamination Cleanliness and care in aseptic technique, eliminating sources for bacterial contamination, are the most effective means for obviating this danger

Some of the febrile reactions after infusions of plasma, were traced to chemical substances (Strumia) dissolved from soft glass used for containers, and some to impurities dissolved from rubber connections in the apparatus The Subcommittee on Blood Substitutes, National Research Council, has issued (1942) a Technical Manual which gives precise detailed instructions concerning methods, apparatus and technique for the preparation of plasma High quality ampoule glass and sulfur-free, non-oxidizing rubber are specified The use of 1 to 15,000 phenyl mercuric borate or of 1 to 10,000 merthiolate is also recommended Those interested in technical details are referred to this manual and to a Technical Manual on the Preservation and Transfusion of Human Whole Blood Both were prepared under the auspices of the National Research Council and were issued by the United States Office of Civilian Defense

It appears that, when carefully obtained and prepared, plasma or serum may be given with equal safety and effectiveness Our British and Canadian colleagues have used and are using serum almost exclusively and with highly satisfactory results, yet they make no claim that it is superior to plasma in any important particular The use of these, under comparable conditions in treating air-raid casualties in England, did not show that the reaction rate of either was consistently higher than the other Best and Solandt have developed an elaborate system by which thousands of pints of blood are collected and the serum separated, tested and desiccated for shipment to England each month They emphasize the point that plasma and serum, if they are free from reaction-producing substances, are therapeutically identical and may be used interchangeably They regard it as regrettable that discussions on the relative merits of these should hinder either their production or their use

Opinion in the United States is divided, a majority appearing to favor the use of plasma The latter has been adopted for military use by the Medical Corps of the United States Army and Navy Hill and Muirhead have reported on the administration of

674 doses of plasma, resulting in only 5 reactions They purposely disregard distinction between plasma and serum as therapeutic agents, and state that a proper preparation of either is an innocuous substance which does not cause reactions

From these and from similar expressions of opinions by others it appears that either product, if properly prepared, is equally useful and free from untoward effects This evaluation is corroborated by the fact that preparations both of serum and of plasma have been accepted as New and Unofficial Remedies by the Council on Pharmacy and Chemistry, and that both have been endorsed and will appear officially as therapeutic agents in the forthcoming edition of the U S Pharmacopœia

The U S Pharmacopœia specifies three means for the storage of these products liquid plasma to be preserved at temperatures between 10° and 20° C , frozen plasma at temperatures between −10° and −20° C , dried plasma, not be exposed to excessive heat. It is recommended that liquid plasma be kept not longer than one year

TWO NOTEWORTHY DEVELOPMENTS

Among the developments which have contributed to the practical management of shock and of hemorrhage, two are so significant as to merit special notice

Desiccated Plasma and Serum.—In 1935 Flosdorf and Mudd developed the "lyophile" method for dehydrating serum and other biologic products from the frozen state They gave due credit to others for preceding developments Subsequently in collaboration with Eagle Stokes and McGuinness they obviated certain disadvantages in the previous method by introducing what is known as "cryochem" process later they devised the "desivac" process. These were the innovations from which have developed several practical methods for obtaining, concentrating preserving and distributing plasma or serum in quantities sufficient for extensive use in civil populations and in military forces in remote areas The full significance and scope of this development has not yet been grasped by the medical profession

Subsequently several practical methods have been perfected for accomplishing the same purpose by different means. Among these should be mentioned the Hill Adtevac process and Hartman's simple and inexpensive method for drying serum or plasma in cellophane bags It is not appropriate to discuss here the technical

procedures and the advantages presented by these and by other methods If the finished product conforms to the specifications set forth in the Pharmacopœia, physicians will use that product with assurance and confidence

The dehydration or complete desiccation of plasma or serum provides several major advantages not otherwise attainable The product will keep for years at ordinary temperatures without deterioration It has small volume which facilitates its transportation and distribution into all areas and localities where the treatment of hemorrhage and shock may be necessary The plasma or serum, bottled and dehydrated in the laboratory where it was processed, can be redissolved with the distilled water packaged with it in from one to three minutes It may be administered promptly under emergency conditions, even in the field, in ambulances and in first aid stations, with needle and other equipment contained in the package

A final advantage of inestimable therapeutic value is that the plasma or serum may be given in any desired concentration or dilution When given in isotonic form, *i e*, neither above nor below the concentration of normal plasma, it merely replaces the depleted blood volume with a suitable fluid having about the same osmotic activity as the patient's blood But when given in *concentrated* form, its osmotic potency tends to reestablish fluid balance It restores the depleted fluid of the blood in part by drawing fluid into it from the tissues This physiologic principle is utilized by giving plasma or serum in from twice to five times the isotonic or normal concentration

Infusions via the Bone Marrow.—A second development of major importance is a simple technique for giving blood and other fluids by injection into the bone marrow All who have attempted venipuncture for any purpose during shock have realized the difficulty of entering veins, large or small, with any type of needle The peripheral veins are so collapsed and bloodless that it may be impossible to cannulate them successfully even by venisection Adiposity of the patient may handicap further the efforts of the operator These difficulties hinder all attempts to restore an adequate blood volume by introducing fluids Much time may be lost in unsuccessful efforts to cannulate vessels and the operation of the vicious circle may be approaching the irreversible stage, moment by moment It often is necessary to incise deeply and expose large vessels, as in the femoral region This procedure may be practical in the operating room or in a well equipped office

but not in first aid posts, in combat areas nor in other circumstances of emergency Even when venisection and cannulation are successful, time is consumed, a wound is made and the procedure is technically more involved than the simple insertion of a needle.

Tocantins found by experiments on cadavers and on animals that dyes injected into the bone marrow enter the venous circulation immediately Accordingly a technique was devised for giving transfusions of blood and other fluids by this route He inserts a short styletted needle, 18 to 20 gage, in the midline of the

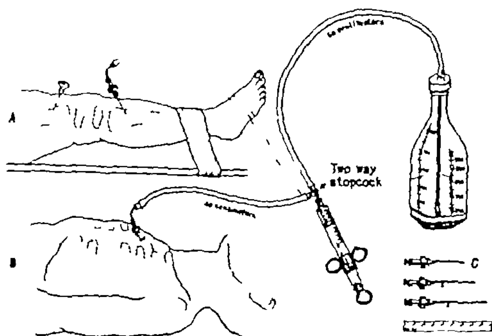


FIG. 28 —A convenient arrangement for the rapid injection of substances A into the bone marrow of the tibia of young children and B of the sternum of adults. C shows convenient sizes of the needles for giving infusion *via* the bone marrow This equipment in a sterile package should be held in readiness in hospitals and emergency stations. (Courtesy of Dr L. M Tocantins.)

sternum at the level of the 2d or 3d interspace The needle is inserted at an angle of about 45° and is simultaneously pushed and rotated with a boring motion until a sudden decreased resistance is noted This indicates that the needle has penetrated the outer plate of the manubrium and is in the marrow space The stylette is then withdrawn a syringe is attached and some marrow fluid is aspirated to indicate with certainty that the opening of the needle is within the marrow space Fluid may then be introduced either by syringe or by a simple type of transfusion apparatus

(see Fig 28) He states that fluid will flow by gravity as readily into the marrow space as into a vein

Tocantins and his associates have reported on the use of this method in 72 patients without any untoward local or systemic effects They have found it advantageous in postoperative circulatory failure, after hemorrhages, in insulin shock, and in giving fluids intravenously to children for any purpose They recommend its use for introducing fluids or drugs whenever veins cannot be entered readily and when the administration of fluid is urgently needed

The advantages of a safe and rapid means for introducing fluids into the blood under difficult circumstances, need no emphasis

THERAPEUTIC USE OF PLASMA OR SERUM

Plasma or serum kept in a liquid state tends to develop varying degrees of flocculation which is more marked in plasma because of its fibrinogen content This requires filtration before use, preferably through a Seitz, glass cloth or other lint-free filter Usually no flocculation occurs in frozen plasma or in the desiccated product when redissolved

Some give plasma or serum diluted with an equal quantity of saline or dextrose solution Elliott, Tatum and Busby have reported excellent results by this method in shock from various causes, after burns, and in the treatment of hypoproteinemia They found this an excellent substitute for whole blood by transfusion in the treatment of hemorrhage White, Collins and Weinstein also favor the use of plasma-saline mixture They reported its use in over 500 cases of various types including 81 instances of shock following surgery or trauma "The results were satisfactory in most cases and in some even spectacular"

This mode of treatment is distinctly superior to the use of saline or dextrose solutions, its usefulness would appear to be greatest in those states in which genuine dehydration of the tissues occurs, as in cholera, dysentery and other conditions in which the water content of the tissues has been markedly reduced Diluted plasma or serum restores the blood volume adequately but the fluid with which it was diluted may escape readily through permeable endothelium and may accomplish only temporary benefit Plasma or serum is superior to saline solutions chiefly because of its high protein content and osmotic properties, this superiority is decreased in proportion to the degree of dilution Concentrated plasma or

serum will be more effective in restoring fluid balance by drawing water from the tissues into the blood

Plasma or serum is usually given in the normal or isotonic concentration An impressive list of authors might be cited who have used this method for treating shock and the effects of hemorrhages with gratifying results. The types of cases reported include hemorrhages, traumatic and postoperative shock burns perforations of viscera, intoxications and infections occurring in civilian hospitals (Levinson Strumia, Elkington D K Hill Lee Harkins, their associates and many others) and wounds crush injuries, hemorrhages and burns incident to air raids and battle casualties as seen in London evacuees from Dunkerque and in Pearl Harbor (Grant, Bywaters, Atkins, Maycock Moorhead and associates) These and other reports on the use of blood proteins of about normal concentration, agree in recording highly satisfactory results The use of plasma in isotonic concentration has been adopted as a standard procedure for the treatment of shock and of hemorrhage by the Medical Corps of the United States Army and Navy (Kendrick and Newhouser)

The practice of giving plasma or serum in isotonic concentration conforms entirely to the principle of replacing the depleted blood volume with the same type of fluid as was lost. The merits of this procedure are established unquestionably by the reports of excellent results in clinical use. But this practice fails to utilize another factor of inestimable advantage in restoring circulatory equilibrium —the osmotic potency of *concentrated* plasma or serum

Under physiologic conditions the fluids of the tissues constitute a reservoir for supplying fluid to the blood as needed The forces which control the shift of fluid in either direction constitute the mechanism of fluid balance Abnormal permeability of endothelium from anoxia or other causes not only upsets this balance making unavailable the reservoir of tissue fluid it leads to an *increase* of tissue fluid *at the expense of the blood* The only effective means as yet available for counteracting this disturbance is to increase the osmotic potency of the blood plasma. Various agents have been employed for accomplishing this without success If given in concentrations *above the normal* plasma or serum provides an ideal physiologic means for correcting in some degree the disturbance of fluid balance The administration of these agents in normal concentration or diluted fails to utilize this physiologic advantage

Best and Solandt stated that serum or plasma is employed for

two main purposes, one of which is to provide fluid, the other to provide the serum proteins "which by their osmotic pressure retain fluid in the blood stream or attract it from the tissues" The clinical application of the latter purpose has been reported by several Lee, Elkington and Rhoads observed that the tissue edema subsided after the administration of plasma in the treatment of burns, this was observed in 6 cases Harper, Osterberg, Priestley and Seldon reported on the use of plasma protein in 1 to 10 solution (about 1 5 x normal) in the treatment of shock. There was a decrease in the hemoconcentration and an actual rise in the amount of circulating plasma protein, these changes were sustained

A large series of cases treated with concentrated plasma, 4 x normal, was recently (1942) reported by Muirhead and Hill They recorded data in 93 cases of shock, many of which were complicated by hemorrhages The results were stated as excellent in 68, good in 9, transient in 11 and poor in 5 In total, 674 doses were given with a reaction percentage of 0 74 Three important uses for concentrated plasma were emphasized (*a*) the rapid restoration of blood volume and the acceleration of the circulation in shock from all causes and after hemorrhages, (*b*) the sustained elevation of the plasma protein level in hypoproteinemia from various causes, and (*c*) the control of fluid balance by the prolonged and powerful osmotic effects of the concentrated plasma They regard the latter feature as of inestimable importance in counteracting the mechanism of shock It reinforces the physiologic mechanism for establishing and maintaining the blood volume, and it interrupts or reverses the operation of the vicious circle They found that concentrated plasma not only relieves edema arising from shock but that edema from other causes was also benefited They concluded that hypertonic plasma is the most effective agent available at the present time for increasing intracapillary osmotic forces

Varying degrees of hypoproteinemia accompany shock from different causes This may be due in part to loss of plasma protein by leakage into the tissues, both locally and systemically, and in part to impairment of the hepatic function of building plasma proteins Varying degrees of hepatic degeneration and necrosis occur incident to shock originating from diverse causes For example, hypoproteinemia is a prominent feature after severe burns, it probably results from a combination of the two causes mentioned

The intravenous introduction of plasma or serum is a direct, logical and effective means for counteracting this deficiency Many of the published reports stress this as one of the advantages of blood proteins in the treatment of shock Hill and others have found it effective also in relieving hypoproteinemia from causes other than shock.

If desiccated plasma or serum were available only as prepared by concerns that manufacture biologic products commercially, the cost would be almost prohibitive Donors require compensation for their contributions of blood the technical procedures for processing it are numerous, intricate and require expensive apparatus, a staff of highly trained operators, including bacteriologists and serologists, is required The mass production of desiccated plasma for use among the armed forces of the nation is possible only because of generous voluntary donations of blood government subsidy for apparatus and personnel, and the coöperation of hospitals and other medical institutions. The American Red Cross has organized and is administering this project which produces units of desiccated plasma by thousands

To what extent this organization will carry on for meeting civilian needs in times of peace is uncertain Groups of hospitals may coöperate in the production of plasma as they have done in maintaining blood banks for transfusion purposes. Developments already made support the hope that a suitable substitute as pectin gelatin or bovine albumin, may be perfected which will be more easily obtained and less costly than products of human blood

Administration —Those having practical experience agree that no uniform scheme for determining the required dosage of plasma or serum has been or can be formulated The amounts required vary extremely in different cases. In a case of mild or incipient circulatory deficiency 250 cc of plasma or the concentrated proteins derived from it may furnish all that is needed but in a case of marked deficiency accompanied by stasis anoxia hemoconcentration and low arterial pressure ten times that dosage may not prevent death

Strumia and McGraw prefer to estimate dosage in terms of protein content rather than in terms of fluid volume given The finished product of desiccated plasma or serum usually is packaged in quantities of 16 to 20 gm each or of 35 to 40 gm each These represent the average amounts of plasma proteins derived

from a single donation or from two donations of blood, respectively Usually about 500 cc of blood is drawn from a donor, this may yield about 250 cc of plasma These authors recommend 35 to 36 gm of plasma protein as an initial dose in shock without hemorrhage Such cases may require two or three additional doses at intervals They state that enough should be given to raise and maintain an adequate volume of circulating blood as evidenced by satisfactory pulse quality, blood pressure and blood concentration This seems to express the opinion prevailing at this time regarding dosage

Severely burned patients require much larger amounts of plasma or serum than are needed in shock from operations or trauma. Muirhead and Hill gave 600 cc of 4 x normal plasma to one patient in severe shock and 1200 cc to a severely burned patient. It has been said that cases of severe burns should receive "plasma and more plasma" Strumia and McGraw reported a case in which about two-thirds of the body surface was burned This patient received a total of 700 gm of dried plasma or the equivalent of 10,000 cc of isotonic plasma, recovery followed. Harkins (175[16]) states that, particularly in burn shock, 100 cc of isotonic plasma should be given for each point the hematocrit reading exceeds 45, as long as the proteins are above 6 gm per 100 cc If the hematocrit reading is 55, the patient should receive 1000 cc. of isotonic plasma or 250 cc of 4 x concentrated plasma

Plasma solution also transfusions of citrated blood are often given slowly by the continuous drip method This is not advisable as the initial treatment in shock It is desirable that the blood volume be raised as soon as may be, this is best accomplished by rapid injection Hill and Muirhead recommend giving 100 cc of fluid in about two minutes when circulatory deficiency is present or threatens

Summary.—The practical management of shock includes the various means discussed *in preceding chapters*, by which it may be prevented or its effects reduced to a minimum.

The rationale of fluid therapy is simple in its basic principles It consists in maintaining the blood volume by replacing, with the same type of fluid if possible, that which was lost

It is of prime importance to distinguish between primary shock, delayed or secondary shock and the effects of hemorrhages. Observations on the concentration of the blood are most useful in the differentiation of these and in determining both the appropriate treatment and the dosage of the fluids to be given.

Saline solutions, with or without glucose, may be of value in the prevention of postoperative shock also after moderate hemorrhages They produce no permanent improvement in secondary shock

Transfusions of whole blood are most useful in combating the effects of serious hemorrhages combined with minor degrees of shock. They are ineffective in counteracting severe shock in which hemorrhage is a minor factor

Plasma or serum given intravenously presents a combination of advantages not otherwise obtainable (1) It restores blood volume by the same type of fluid as was lost (2) It does not escape readily by leakage unless grave injury to endothelium has occurred (3) Concentrated plasma or serum has a high osmotic pressure which draws fluid from the tissues into the circulation this helps to reëstablish fluid balance and counteracts the mechanism by which shock progresses (4) It restores directly the low plasma protein which develops incident to shock

Solutions of acacia, pectin or purified gelatin should be used only in emergencies when neither whole blood, plasma nor serum is obtainable The development of other substitutes is in the experimental stage.

Speed of administration is of the highest importance when shock is present or is developing The introduction of concentrated plasma or serum into marrow spaces by means of a syringe makes possible the emergency treatment of patients in combat areas first aid stations, even in ambulances or under other circumstances in which intravenous therapy is difficult or impossible

No set rules for treatment or for dosage can be formulated The physician must be cognizant of the requirements of the individual case The dosage of blood by transfusion, or of serum or plasma, must be adequate to relieve the circulatory deficiency This can best be determined by the clinical signs and by the results of simple examinations of the patient's blood

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